

SORTILIN MODULATORS

FIELD OF THE INVENTION

The invention relates to compounds of Formula (I) or (II), which have surprisingly
5 been found to modulate the activity of sortilin. The invention also relates to
pharmaceutical compositions comprising these compounds, and to their use in the
treatment or prevention of medical conditions in which modulation of sortilin
activity is beneficial. In particular, the compounds of the invention may cross the
blood brain barrier and may therefore be particularly useful in the treatment of
10 diseases of the central nervous system.

BACKGROUND

Sortilin is a Type I transmembrane protein that acts as a receptor of several ligands
(Petersen et al., 1997). Sortilin is abundantly expressed in neurons and microglia
of the nervous system, the inner ear, and in some peripheral tissues involved in
15 metabolic control (Tauris et al., 2020; Goettsch et al., 2017; Willnow et al., 2011;
Kjolby et al., 2010). Besides acting as a receptor involved in signaling, sortilin
mediates sorting of select cargo between the cell surface trans-Golgi network, and
endosomal pathway (Nykjaer & Willnow, 2012; Willnow, Petersen, & Nykjaer,
2008). Sortilin harbors a large extracellular domain denoted VPS10 that defines
20 the family of receptors named sortilins or VS10p domain receptors. The VPS10P
domain in sortilin is homologous to yeast VPS10P and is made up by a 10-bladed
beta-propeller structure and a cysteine-rich 10CC module (Nykjaer & Willnow,
2012; Zheng, Brady, Meng, Mao, & Hu, 2011).

Sortilin binds multiple ligands, including pro-nerve growth factor (pro-NGF), pro-
25 BDNF, pro-neurotrophin-3, neurotensin, and ApoB (Chen et al., 2005; Kjolby et
al., 2010; Mazella et al., 1998; Nykjaer et al., 2004; Quistgaard et al., 2009; Yano,
Torkin, Martin, Chao, & Teng, 2009). Furthermore, Sortilin binds progranulin
(PGRN), a secreted protein involved in many cellular functions including securing
lysosomal processes, anti-inflammatory responses, and neurotrophic stimulation
30 (Galimberti, Fenoglio, & Scarpini, 2018). Sortilin targets PGRN for rapid

endocytosis and degradation, and it is now well established that sortilin is the most important clearance receptor for PGRN (Hu et al., 2010). Thus, sortilin negatively regulates the extracellular levels of PGRN in the periphery as well as in the brain. Indeed, lack of or blocking the receptor increases plasma PGRN levels both in
5 mice and humans (Carrasquillo et al., 2010; Gass, Prudencio, Stetler, & Petrucelli, 2012; Hu et al., 2010; Lee et al., 2014; Miyakawa et al., 2020; Pottier et al., 2018).

Frontotemporal dementia is a highly heritable dementia and haploinsufficiency of the PGRN gene accounts for up to 25% of all cases (Gijssels, Van Broeckhoven, & Cruts, 2008). Patients with heterozygous loss-of-function mutations in PGRN
10 have >50% reduced extracellular levels of the protein and will invariably develop FTD, making PGRN a causal gene for the disease (Baker et al., 2006; Carecchio et al., 2011; Cruts & Van Broeckhoven, 2008; Galimberti et al., 2010). In addition, PGRN mutant alleles have been identified in Alzheimer's (AD) patients (Brouwers et al., 2008; Sheng, Su, Xu, & Chen, 2014) and high levels of extracellular PGRN
15 are protective in models of ALS, Parkinson's disease, stroke, arthritis, and atherosclerosis (Egashira et al., 2013; Laird et al., 2010; Martens et al., 2012; Tang et al., 2011; Tao, Ji, Wang, Liu, & Zhu, 2012; Van Kampen, Baranowski, & Kay, 2014).

Sortilin is, however, not required for PGRN to elicit its functions. Hence, neurons
20 devoid in sortilin expression are equally responsive to PGRN-induced neuronal outgrowth (De Muijnck et al., 2013; Gass, Lee, et al., 2012). Further, PGRN is successfully delivered to neuronal lysosomes in sortilin-deficient cells, suggesting the existence of alternative trafficking pathways. Indeed, PGRN can bind to the lysosomal protein, prosaposin (PSAP). When PSAP binds to its cognate
25 receptors, the cation-independent mannose-6-phosphate receptor and LRP1, it brings along PGRN to the lysosomes (Zhou et al., 2015). Finally, in a phase II clinical trial with a monoclonal anti-sortilin antibody, markers for lysosomal integrity were normal (NCT03987295).

The functional PGRN receptor remains to be identified. However, studies suggest
30 that PGRN promotes neuronal survival, reduces inflammation and increases A β

endocytosis by microglia (Martens et al., 2012; Pickford et al., 2011; Yin et al., 2010).

Binding of PGRN to sortilin requires the three amino acids in the C-terminal of PGRN (QLL in human, PLL in mouse), and a peptide derived from the last 24 amino acids of PGRN binds with similar affinity as the full-length protein (Zheng et al., 2011). It was proposed that this mode of binding is structurally similar to Neurotensin binding (Zheng et al., 2011), i.e. binding in the NTIS1 binding site of sortilin. There has been a successful small molecule screen that identified a blocker of Neurotensin to sortilin binding done in collaboration with Aarhus University (Andersen et al., 2014; Schroder et al., 2014).

Sortilin exists as a full-length and sorting competent receptor but is also capable of forming multimeric signalling receptor-ligand. Portions of sortilin can also be liberated from the plasma membrane to scavenge ligands (NT in pain) and control the activity of ligands. For example, sortilin is involved in synaptic plasticity by controlling the conversion rate of pro-BDNF into BDNF. This may also apply to other proneurotrophins.

Finally, the propeptide of sortilin, also named spadoin, that is a ligand of the receptor has been demonstrated to control the activity of the membrane transporter TREK-1, which is a target for major depression, among other diseases. Structurally, sortilin has an amino acid sequence according to SEQ ID NO: 1 and comprises a signal peptide, a propeptide, the Vps10p domain, a 10cc domain (10CCa + 10CCb), a transmembrane domain and a cytoplasmic tail. The luminal domain of sortilin has 6 potential *N*-linked glycosylation sites, whilst the cytoplasmic tail enables for the recruitment of various adapter proteins.

Sortilin binds to a vast number of ligands and membrane receptors and as a result engages in functions known to be important in cellular signalling and sorting. For example, sortilin is involved in signalling by proneurotrophins: the proforms of nerve growth factor (pro-NGF), brain derived neurotrophic factor (pro-BDNF), and neurotrophin-3 (proNT3), respectively. In complex with the protein p75NTR (p75 neurotrophin receptor), sortilin has been reported to form the receptor for

proneurotrophin-mediated apoptotic effects leading to degeneration and cell death in cellular and animal models (Jansen et al., 2007; Tenk et al., 2005; Nykjaer et al., 2004).

Previous work has suggested a role for sortilin in cellular sorting and signalling associated with diseases such as diabetes and obesity (Huang et al., 2013). Sortilin facilitates translocation of GLUT4 to the plasma membrane and rescues it from degradation in the lysosomes (Pan et al., 2017). Sortilin levels have been shown to be modulated by the level of inflammation associated with these diseases. The pro-inflammatory cytokine, TNF α , reduces both mRNA levels and protein levels of sortilin in cultured mouse and human adipocytes, as well as *in vivo* when injected into mice (Kaddai et al., 2009). Sortilin can also influence cytokine secretion: targeting sortilin in immune cells has been proposed to attenuate inflammation and reduce atherosclerosis disease progression (Mortensen et al., 2014). Additionally, US 2016/0331746 describes various scaffolds of small molecules capable of binding to the active site of sortilin. Sortilin is involved in the regulation of glucose uptake (Shi & Kandror, 2005) and the development of lipid disorder diseases (Gao et al., 2017).

Further, plasma sortilin levels have been reported to be a potential biomarker for identifying patients with either coronary heart disease or diabetes mellitus (Oh et al., 2017; Møller et al., 2021). Patients that showed increased sortilin levels within their plasma, and therefore identifiable as suffering from the above conditions, also displayed enhanced glucose levels suggesting sortilin as a therapeutic target for treating these conditions. Soluble sortilin is also proposed as a treatment for type II diabetes (WO2021116290 A1, 2021).

TAR DNA-binding protein 43 (TDP-43) has been implicated in various neurodegenerative diseases. For example, TDP-43 inclusion bodies have been found in cases of amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), and Alzheimer's disease (AD) (Meneses et al., 2021).

TDP-43 regulates the splicing of several gene products, including Sortilin. In humans, the splicing involves inclusion of a cryptic exon 17b (between exon 17

and 18), which introduces a stopcodon in the stalk, potentially generating a non-membrane bound fragment (Prudencio et al., 2012). Furthermore, it has been shown that PGRN can reduce levels of insoluble TDP-43 and slow down axonal degeneration (Beel et al., 2018). Sortilin inhibition increases PGRN levels and is
5 therefore beneficial in the treatment of neurodegenerative diseases in which TDP-43 is implicated.

Sortilin has been linked to various conditions affecting the central nervous system (CNS). Some studies suggest a role of circulating sortilin in patients with psychiatric disorders such as depression, which may relate to altered activity of
10 neurotrophic factors (Buttenshon et al., 2015); and it has also been reported that sortilin plays a role in brain aging, Alzheimer's Disease and frontotemporal dementia (Xu et al., 2019). However, delivering therapeutic agents that are capable of crossing the blood-brain barrier to the CNS presents a major challenge.

The blood-brain barrier is a highly selective semipermeable border of endothelial
15 cells that prevents solutes in the circulating blood from non-selectively crossing into the extracellular fluid of the CNS where neurons reside. Therapy of neurological diseases is therefore limited due to the restricted penetration of therapeutic agents across the blood-brain barrier.

Therapeutic agents for treating CNS diseases therefore must be capable of
20 crossing the blood-brain barrier. In addition to this, they must also have a sufficient unbound drug concentration in the brain, as the free drug hypothesis states that only unbound compound is able to interact with and elicit a pharmacological effect.

To determine the unbound fraction of a test compound (F_{ub}), sample supernatants may be analysed by methods such as liquid chromatography with tandem mass
25 spectrometry (LC-MS/MS). The unbound fraction may then be calculated from the peak area ratios obtained for each matrix according to the following formula:

$$F_{ub} = C_{PBS} / C_{plasma}$$

where C_{PBS} and C_{plasma} are the analyte concentrations in PBS (receiver) and plasma (donor), respectively.

Recovery samples may be prepared in each condition but without dialysis, and may be used for evaluation of recovery from dialysis experiments using the following formula:

$$\% \text{ Recovery} = 100 \times (V_{\text{PBS}} \times C_{\text{PBS}} + V_{\text{plasma}} \times C_{\text{plasma}}) / V_{\text{plasma}} \times C_{\text{recovery}}$$

where V_{PBS} is the volume on the receiver side (PBS) and V_{plasma} is the volume on donor side (plasma) of the dialysis device. C_{recovery} is the analyte concentration measured from the recovery sample. Compounds such as propranolol or fluoxetine, may be included in experiments as controls.

- 10 The unbound fraction in brain ($F_{\text{ub, brain}}$) may be calculated from the measured value in brain homogenate ($F_{\text{ub, meas}}$), taking into account the dilution factor used in preparing the brain homogenate:

$$F_{\text{ub, brain}} = \frac{1/D}{\left(\frac{1}{F_{\text{ub, meas}}}\right) - 1 + \left(\frac{1}{D}\right)}$$

where D = dilution factor.

- 15 The brain/plasma unbound partition coefficient (K_{puu}) may be determined as a ratio between the free compound concentrations in plasma and brain:

$$K_{\text{puu}} = \frac{C_{\text{ub, brain}}}{C_{\text{ub, plasma}}}$$

Where $C_{\text{u, brain}}$ = unbound concentration in brain ($C \times F_{\text{ub, brain}}$); wherein

C = concentration at steady state; and

- 20 $C_{\text{ub, plasma}}$ = unbound concentration in plasma ($C \times F_{\text{ub}}$).

Alternatively a ratio of AUCs can be used to determine K_{puu} . The compound of interest being dosed to a relevant species of interest at a known concentration by oral or intravenous route. Timecourses of concentration of compound in the

plasma and cerebral spinal fluid (CSF) are measured. The plasma concentration is corrected to account for unbound fraction of compound. Areas under the CSF concentration curve and free fraction in plasma concentration curve are calculated by known methods and a ratio is determined to give:

5
$$K_{puu} = AUC_{0-infcsf} / (AUC_{0-infplasma} \times (\%F_{uplasma}/100))$$

For the treatment of CNS diseases, it is desirable for the K_{puu} to have the highest possible value, above 0. A value around 1 indicating that the free fraction compound freely permeates the blood brain barrier; a value above 1 suggesting that an active influx transport mechanism at the blood brain barrier is involved; and less than 1, which indicates that the free fraction compound is either poorly permeable or is recognized by an active efflux mechanism, reducing the exposure in the CNS while passing back through the blood-brain barrier to plasma or the CSF. A K_{puu} value of 0 or close to 0, indicates a poorly permeable compound or a highly active efflux mechanism that in any case will make highly improbable to reach a meaningful exposure in the CNS of the desired active species.

In view of the above, there is an unmet need for compounds that may be used in the treatment and prevention of medical conditions in which modulation of sortilin is beneficial. In particular, there is an unmet need for sortilin modulators that are capable of crossing the blood brain barrier and are therefore useful in the treatment of diseases of the central nervous system.

BRIEF DESCRIPTION OF FIGURES

Figure 1 is a graph depicting the level of Example 3 in microdialysis samples from the hippocampus of adult male Sprague Dawley rats following oral administration of the compound, corrected for 69.8% probe recovery.

25 Figure 2 is a graph depicting the level of Example 3 in plasma of adult male Sprague Dawley rats following oral administration of the compound.

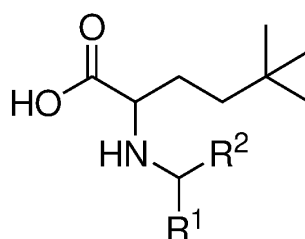
Figure 3 is a graph depicting the relative pharmacodynamic response of PGRN in hippocampal microdialysates of adult male Sprague Dawley rats following oral administration of vehicle or Example 3.

Figure 4 is a graph depicting the level of PGRN in plasma of adult male Sprague
5 Dawley rats following oral administration of Example 3.

DISCLOSURE OF THE INVENTION

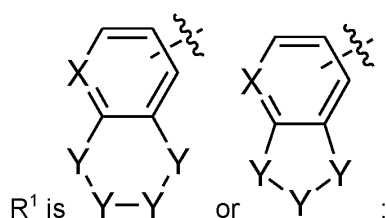
Surprisingly, it has been found that compounds of Formula (I) and (II) modulate the activity of sortilin and are therefore useful in the treatment or prevention of conditions in which modulation of sortilin is beneficial. Furthermore, the
10 compounds may cross the blood brain barrier and may therefore be particularly useful in the treatment of diseases of the central nervous system.

In a first aspect of the invention, there is provided a compound of Formula (I):



(I)

15 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug thereof; wherein

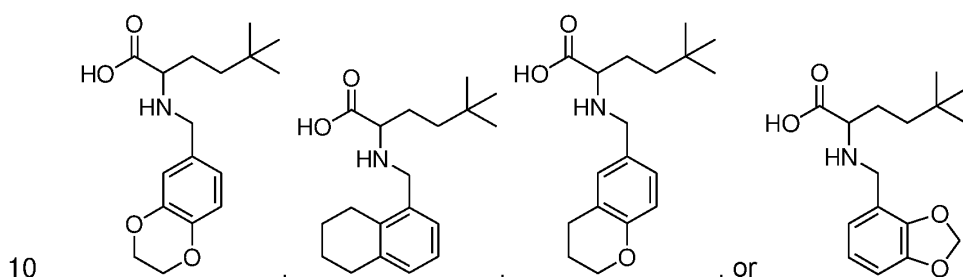


X is CR³ or N, wherein R³ is selected from the group consisting of H, halo, and C₁-C₃ alkyl;

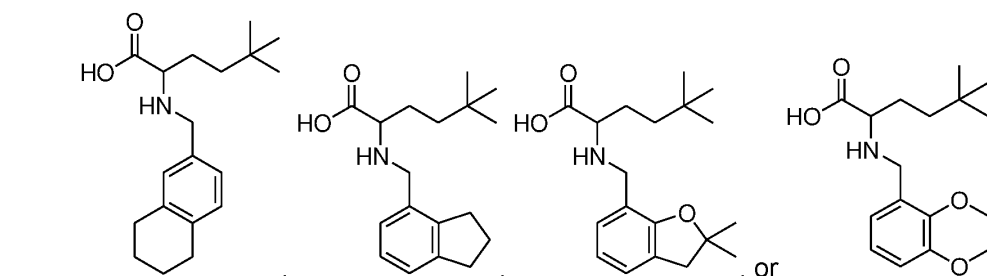
each Y is independently CHR^4 , NR^5 , CR^6R^6 , $\text{C}(\text{O})$, or O , wherein R^4 is independently selected from the group consisting of H, halo, and C_1 - C_4 alkyl; R^5 is independently selected from the group consisting of H, halo, C_1 - C_4 alkyl, C_2 - C_4 hydroxyalkyl, $-(\text{C}_2\text{-C}_4 \text{ alkyl})\text{-O-(C}_1\text{-C}_4 \text{ alkyl)}$, $-\text{C}(\text{O})\text{-(C}_1\text{-C}_4 \text{ alkyl)}$,
 5 and $-\text{C}(\text{O})\text{O-(C}_1\text{-C}_4 \text{ alkyl)}$; and R^6 is independently selected from the group consisting of halo and C_1 - C_4 alkyl;

R^2 is selected from the group consisting of: H, C_1 - C_4 alkyl, C_2 - C_4 hydroxyalkyl and C_1 - C_3 haloalkyl;

wherein the compound is not one of the following compounds:



Preferably, the compound of formula (I) is not one of following compounds:



R^2 is preferably selected from the group consisting of H, CH_3 , CH_2F , CHF_2 , and CF_3 , more preferably R^2 is selected from the group consisting of H, CH_3 , CHF_2 ,
 15 and CF_3 .

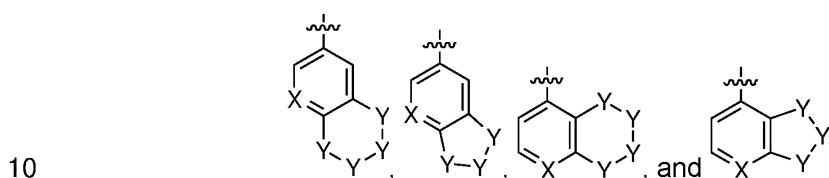
R^3 is preferably H or C_1 - C_3 alkyl, more preferably H or methyl.

Each R^4 is preferably H.

Each R⁵ is preferably independently H, C₁-C₃ alkyl, or -C(O)O-(C₁-C₄ alkyl), more preferably H, methyl, or -C(O)O-(tert-butyl), more preferably H or methyl, most preferably H.

As defined above, each Y is independently CHR^4 , NR^5 , CR^6R^6 , $\text{C}(\text{O})$, or O . In one
5 aspect of the invention, each Y may independently be CHR^4 , NR^5 , CR^6R^6 , or O .

As defined above, R¹ is a partially saturated fused bicyclic ring system. The ring system may be attached to the remainder of the molecule at any suitable position on the aromatic ring. However, in a particularly preferred aspect of the invention, R¹ is selected from one of the following groups:

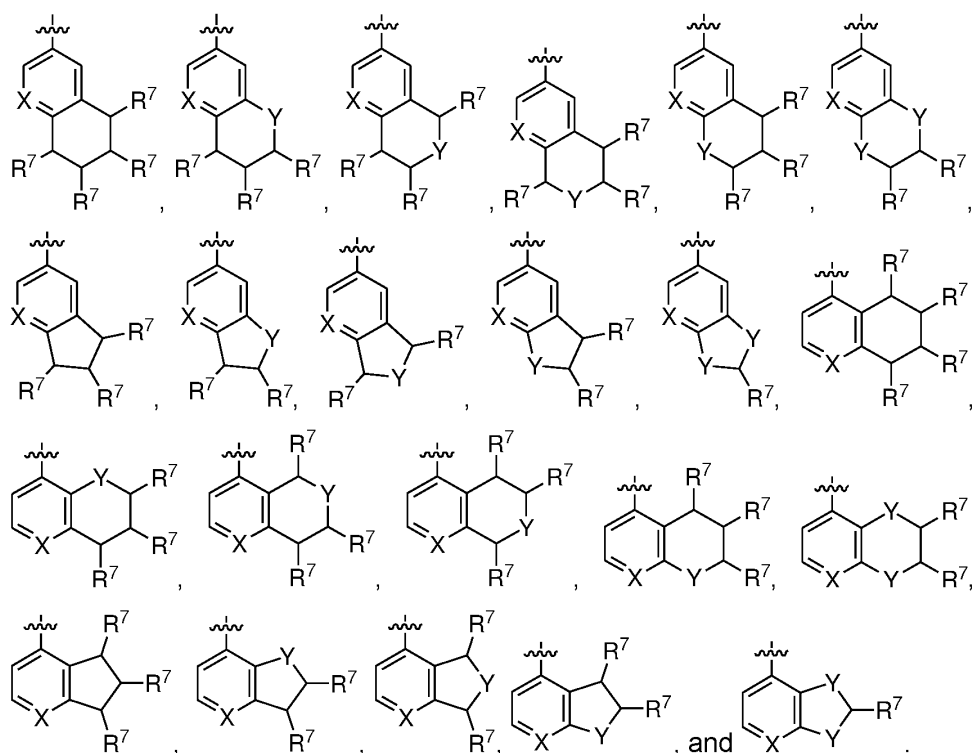


The partially saturated ring of the R¹ group may comprise one or more heteroatoms. However, it is preferred that no more than two atoms in the partially saturated ring are heteroatoms. Therefore, no more than one or two Y are preferably NR⁵ or O and the remaining Y are preferably C(O), CHR⁴, or CR⁶R⁶.

15 The carbon atoms in the partially saturated ring of the R¹ group may be substituted with one or two substituents as defined above. However, it is preferred that any carbon atoms in the partially saturated ring are substituted with no more than 1 substituent. Therefore, if a ring atom in the partially saturated ring is carbon, it is preferably C(O) or CHR⁴.

20 Therefore, in a particularly preferred aspect of the invention, no more than two Y are NR⁵ or O and the remaining Y are independently C(O) or CHR⁴.

Preferable examples of the R¹ group include:



- 5 In the preferred R^1 groups above, each Y is independently NR^5 or O. However, when the partially saturated ring comprises two Y atoms, it is preferred that one Y is O and the other Y is O or N.

Each R^7 is independently selected from the group consisting of H, halo, and C_1 - C_4 alkyl or the R^7 together with the carbon atom to which it is attached forms an oxo group.

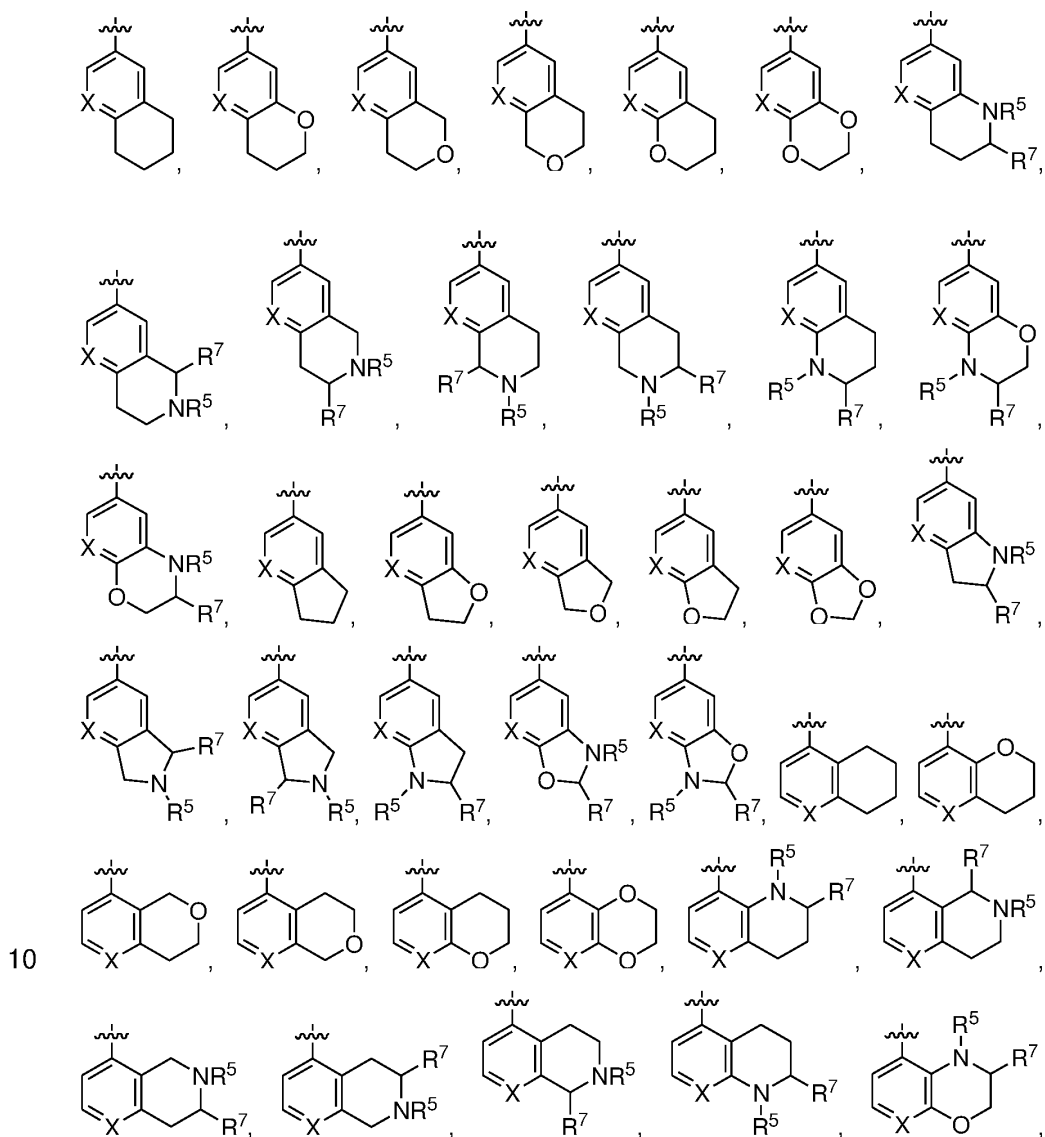
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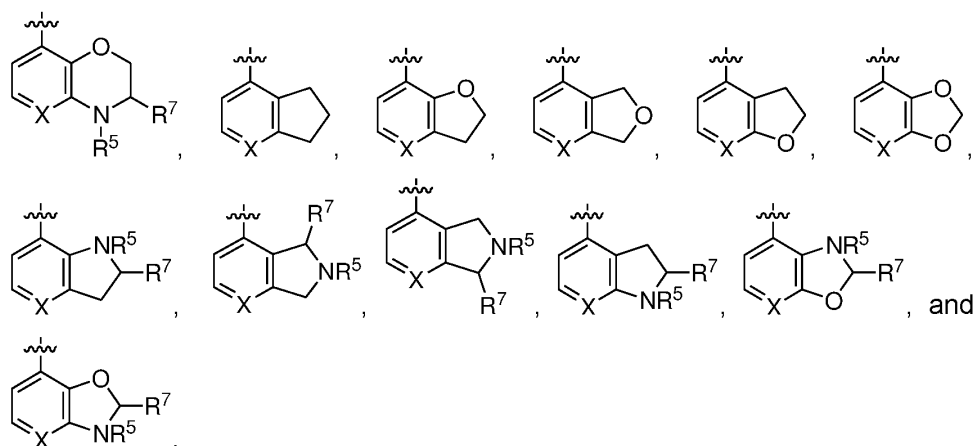
It is also preferred that only one of the carbon atoms in the partially saturated ring is substituted with a substituent. Therefore, one R^7 group is preferably selected from the group consisting of H, halo, and C_1 - C_4 alkyl or the R^7 together with the carbon atom to which it is attached forms an oxo group, and any other R^7 groups are all H. More preferably, one R^7 group is H or the R^7 together with the carbon atom to which it is attached forms an oxo group, and any other R^7 groups are all H.

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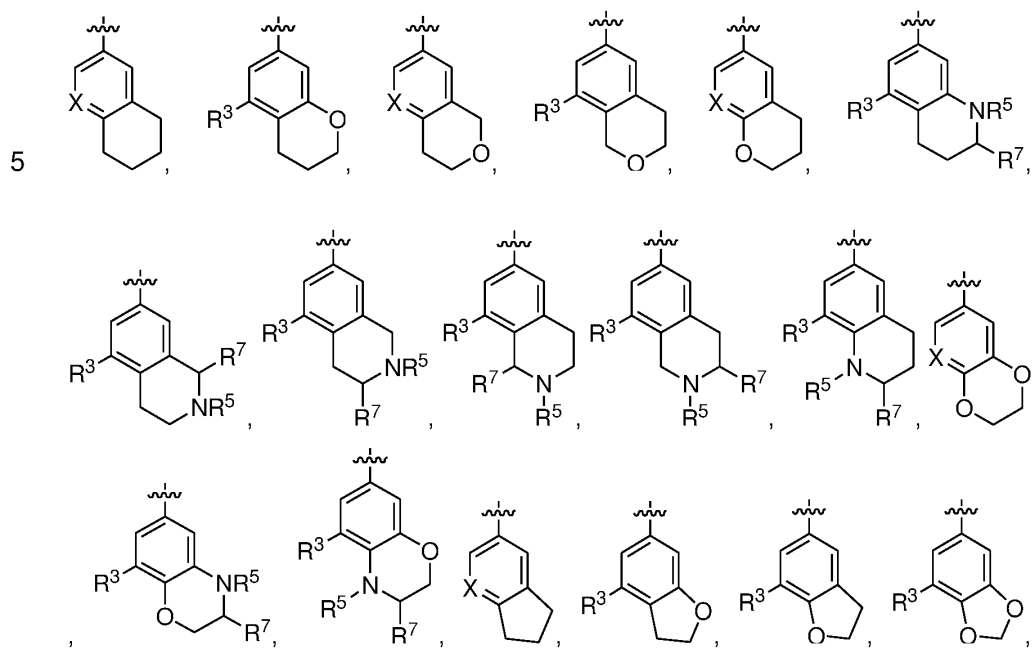
In the compounds of formula (I), when the R^1 group is attached to the remainder of the molecule at the position ortho- to the saturated ring, X may be CH and Y may be O.

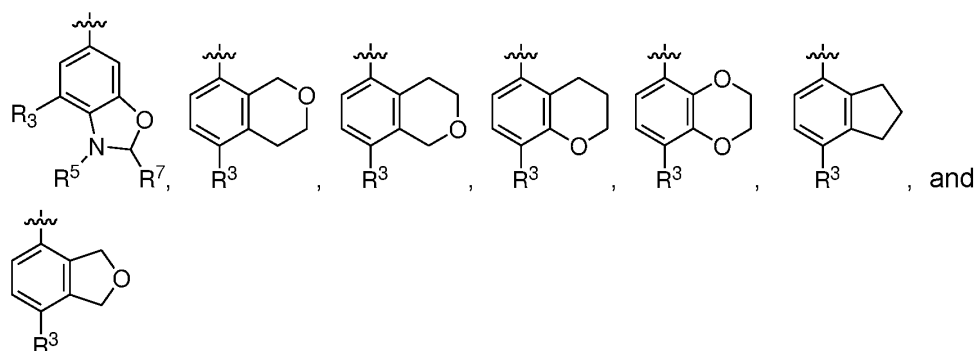
In a more preferred aspect of the invention, R^1 is selected from one of the following groups:



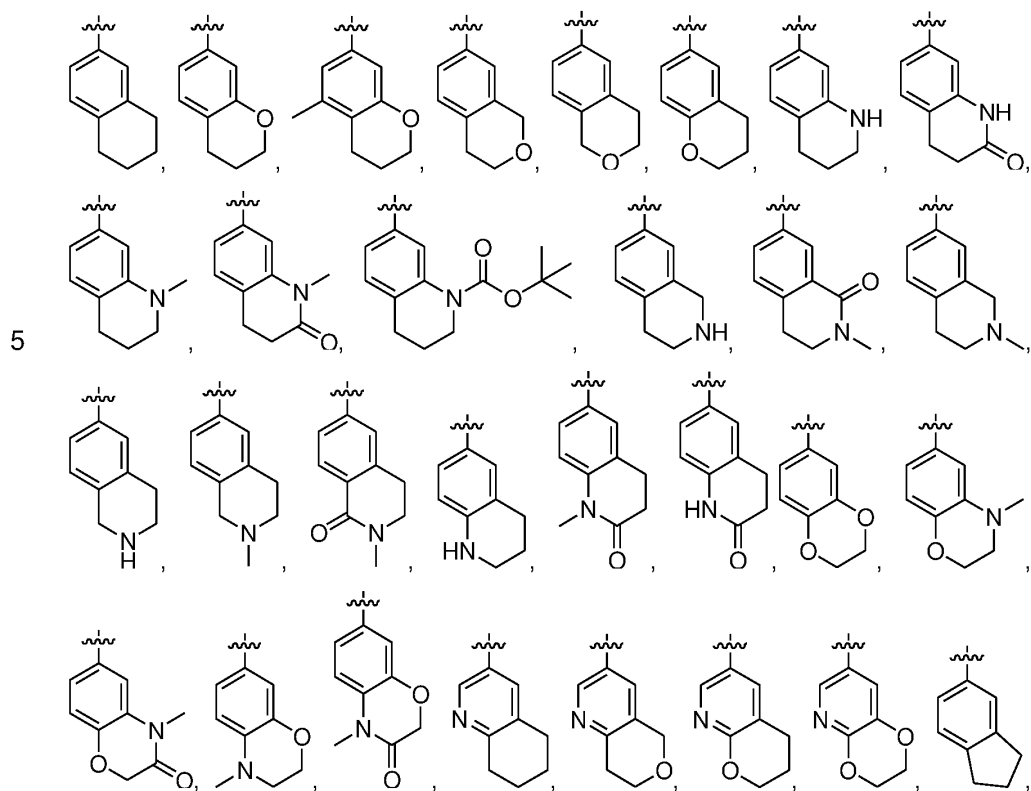


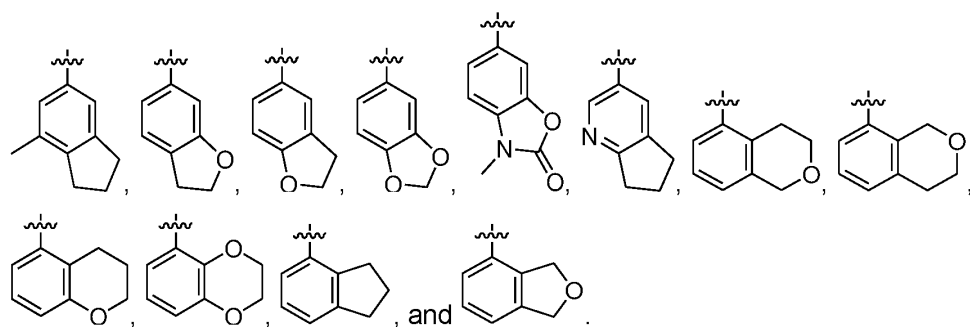
More preferably, R¹ is selected from one of the following groups:



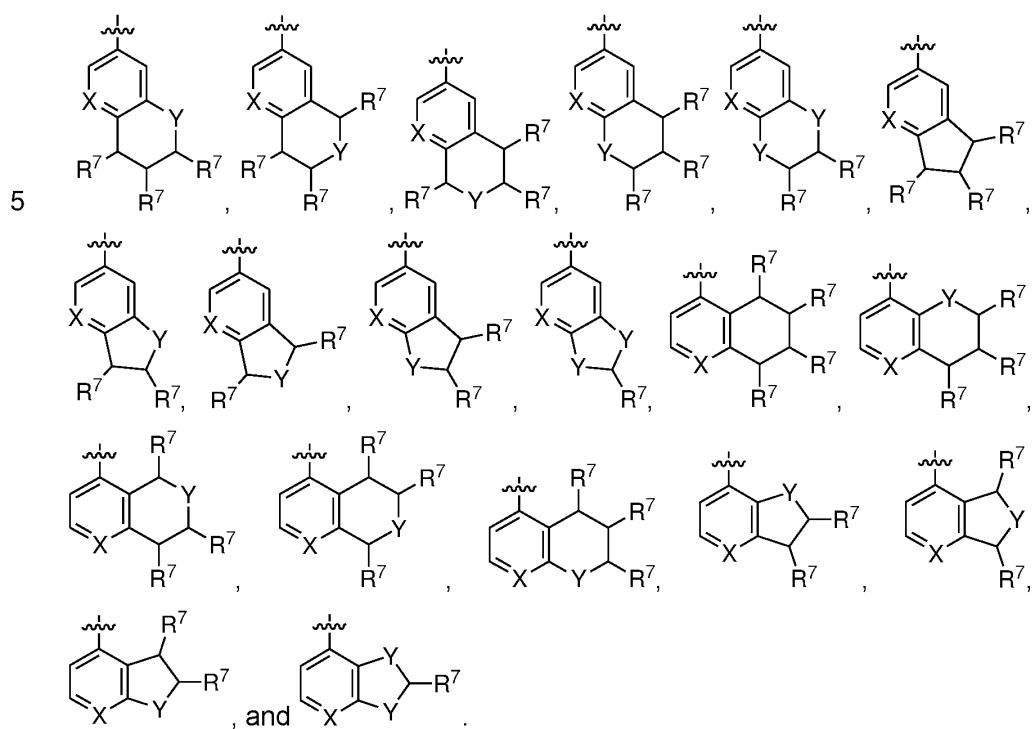


Most preferably, R^1 is selected from one of the following groups:

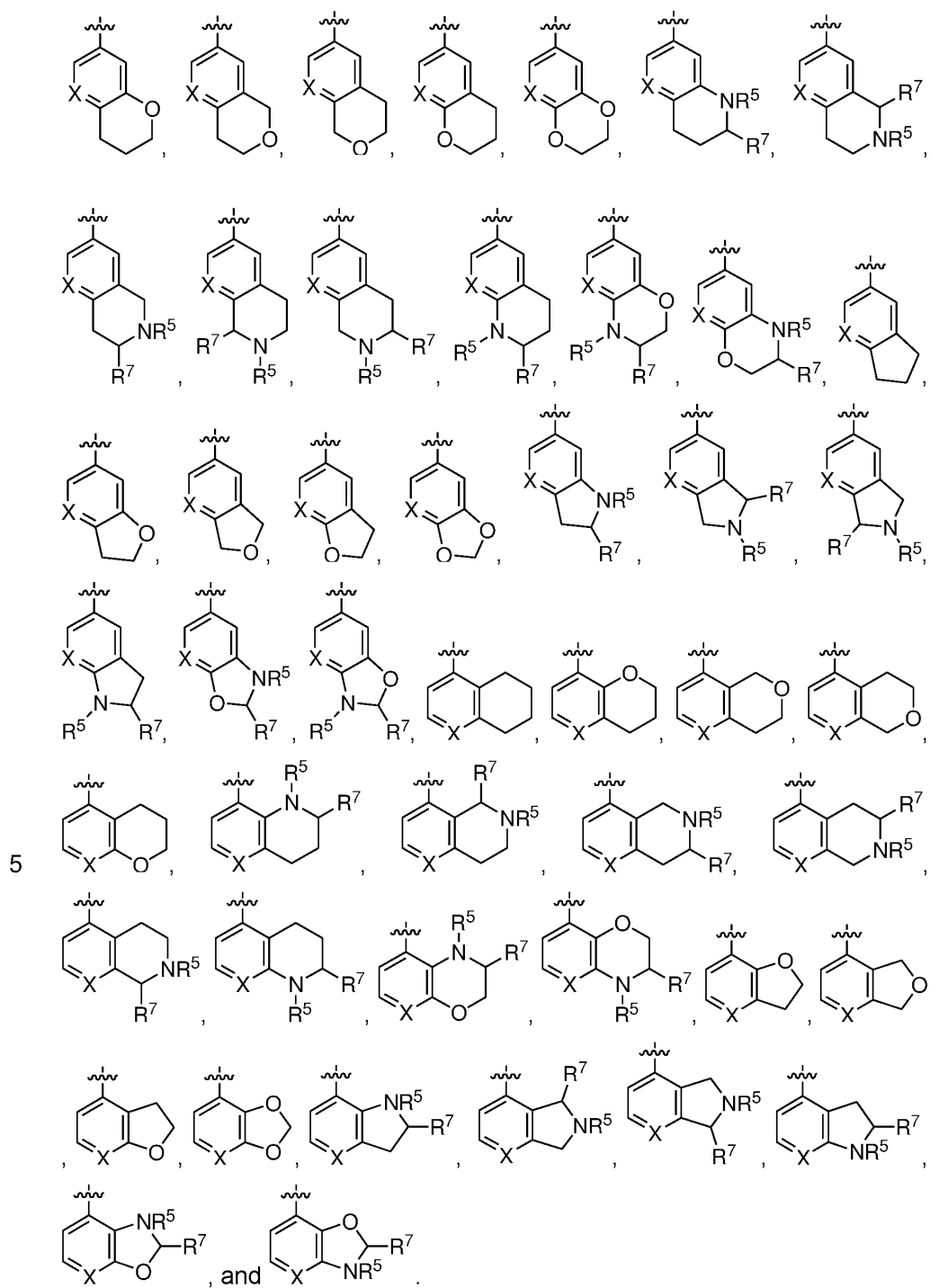




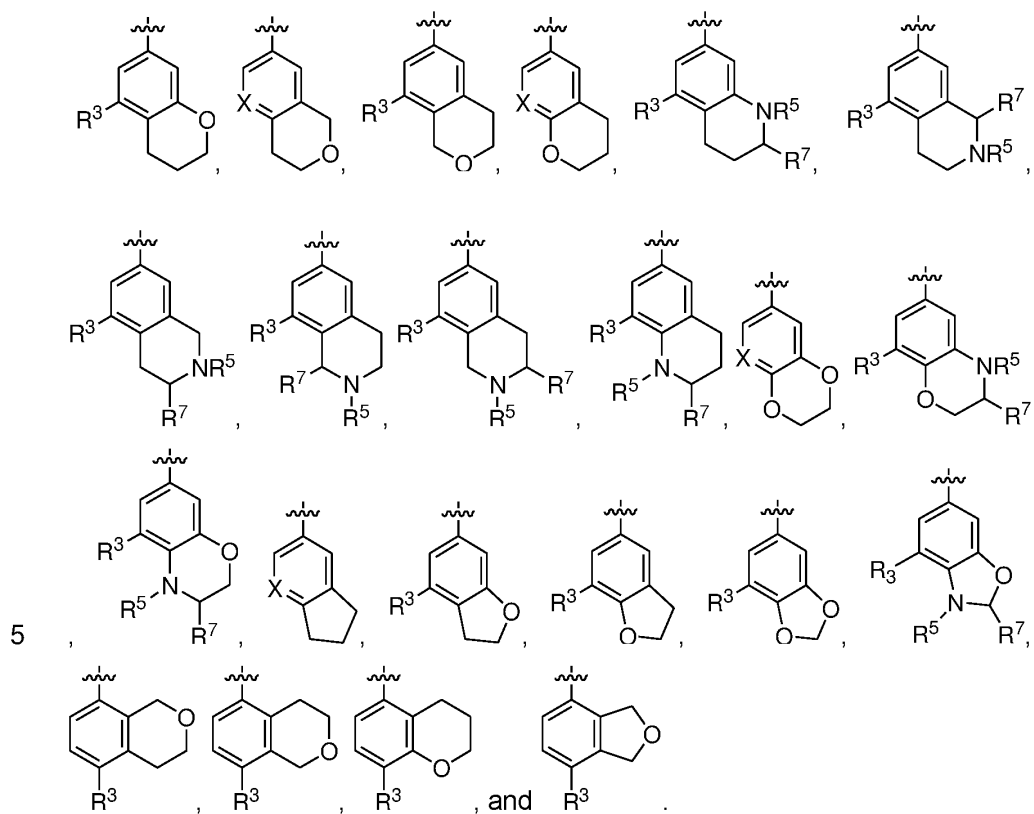
In another preferred aspect of the invention, R^1 is selected from one of the following groups:



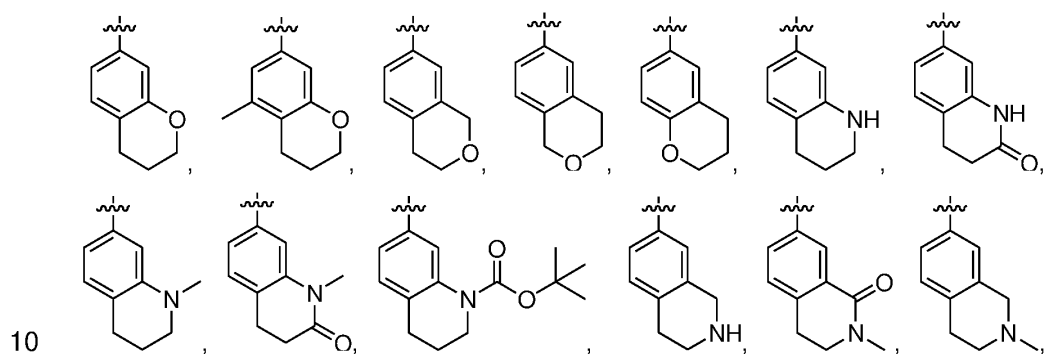
10 In another preferred aspect of the invention, R^1 is selected from one of the following groups:

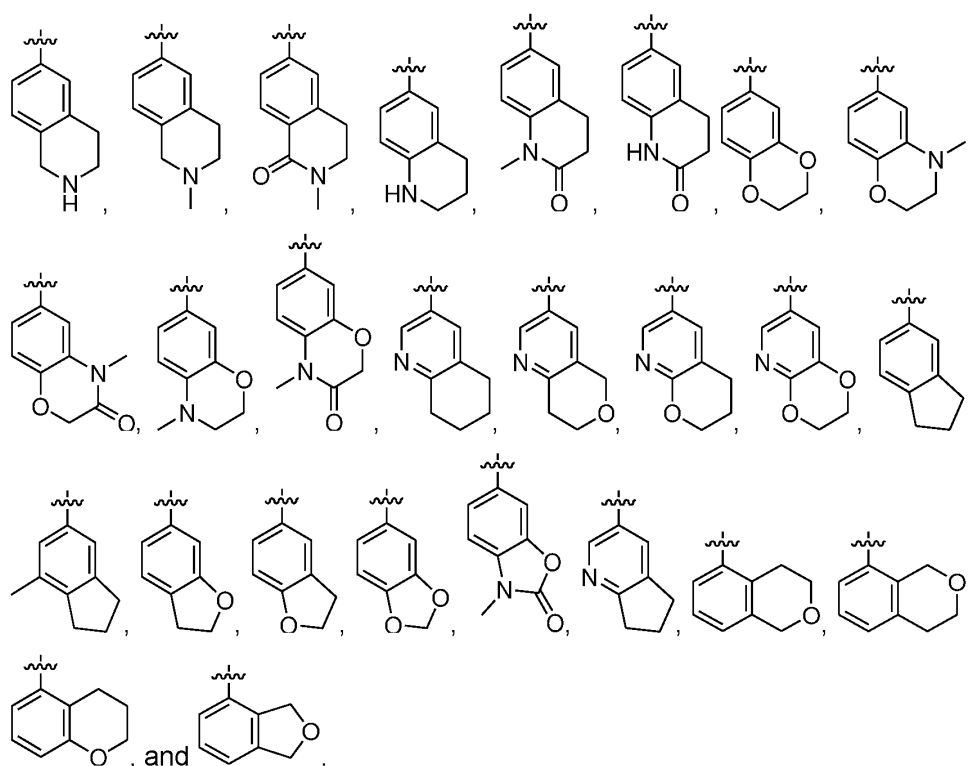


In another preferred aspect of the invention, R^1 is selected from one of the following groups:



In another preferred aspect of the invention, R^1 is selected from one of the following groups:

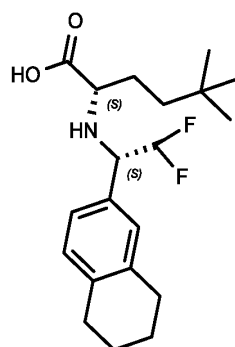




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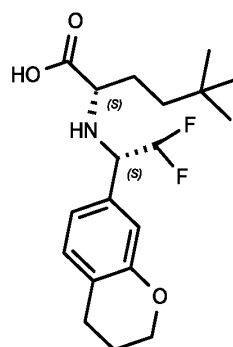
Particular compounds of the first aspect of the invention are those listed below.

- (2S)-2-[[[(1S)-2,2-difluoro-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino]-5,5-dimethylhexanoic acid:

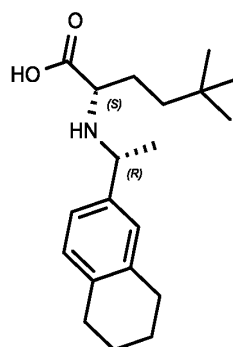


- 10 • (2S)-2-[[[(1S)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)-2,2-difluoroethyl]amino]-5,5-dimethylhexanoic acid:

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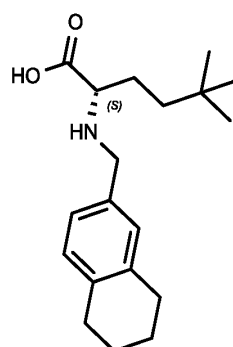


- (2S)-5,5-dimethyl-2-[(1R)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino}hexanoic acid:



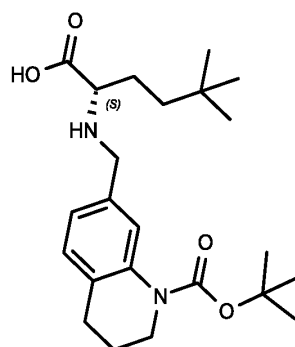
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- (2S)-5,5-dimethyl-2-[(5,6,7,8-tetrahydronaphthalen-2-yl)methyl]amino}hexanoic acid:

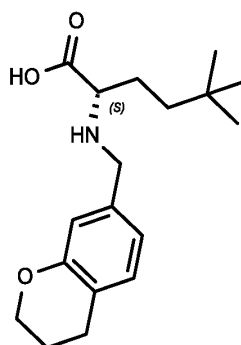


- (2S)-2-[(1-[(tert-butoxy)carbonyl]-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino]-5,5-dimethylhexanoic acid:

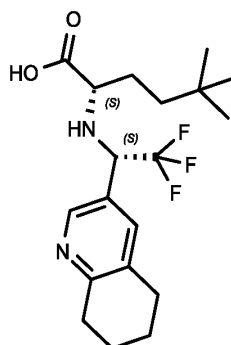
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- (2S)-2-([(3,4-dihydro-2H-1-benzopyran-7-yl)methyl]amino)-5,5-dimethylhexanoic acid:

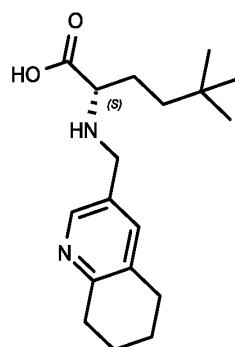


- 5 • (2S)-5,5-dimethyl-2-([(1S)-2,2,2-trifluoro-1-(5,6,7,8-tetrahydroquinolin-3-yl)ethyl]amino)hexanoic acid:

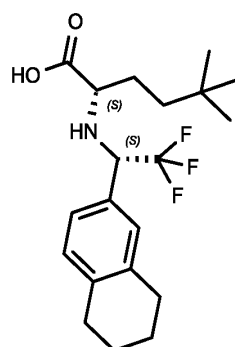


- (2S)-5,5-dimethyl-2-([(5,6,7,8-tetrahydroquinolin-3-yl)methyl]amino)hexanoic acid:

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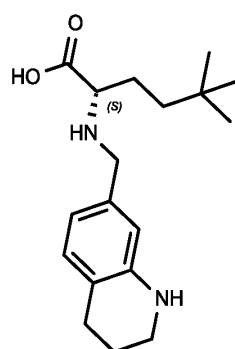


- (2S)-5,5-dimethyl-2-[(1S)-2,2,2-trifluoro-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino}hexanoic acid:



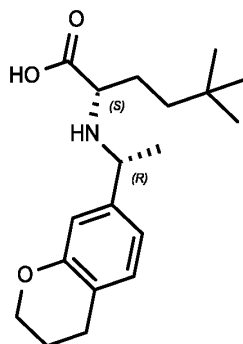
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- (2S)-5,5-dimethyl-2-[(1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino}hexanoic acid:

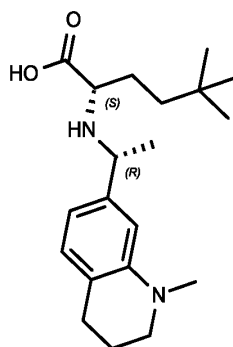


- (2S)-2-[(1R)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)ethyl]amino}-5,5-dimethylhexanoic acid:

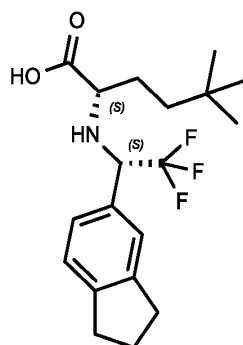
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- (2S)-5,5-dimethyl-2-[(1R)-1-(1-methyl-1,2,3,4-tetrahydroquinolin-7-yl)ethyl]amino}hexanoic acid:

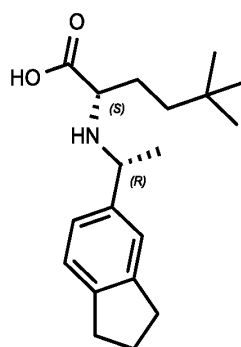


- 5 • (2S)-2-[(1S)-1-(2,3-dihydro-1H-inden-5-yl)-2,2,2-trifluoroethyl]amino}-5,5-dimethylhexanoic acid:

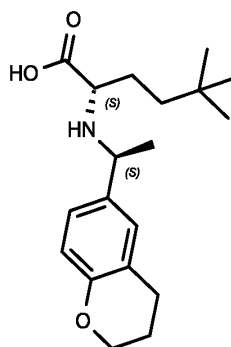


- (2S)-2-[(1R)-1-(2,3-dihydro-1H-inden-5-yl)ethyl]amino}-5,5-dimethylhexanoic acid:

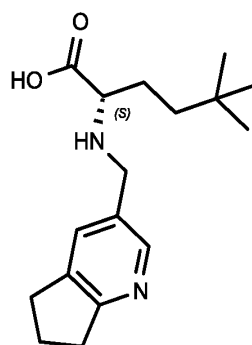
23



- (2S)-2-([(1S)-1-(3,4-dihydro-2H-1-benzopyran-6-yl)ethyl]amino)-5,5-dimethylhexanoic acid:

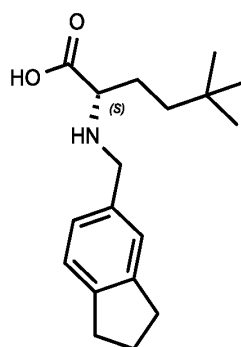


- 5 • (2S)-2-([(5H,6H,7H-cyclopenta[b]pyridin-3-yl)methyl]amino)-5,5-dimethylhexanoic acid:

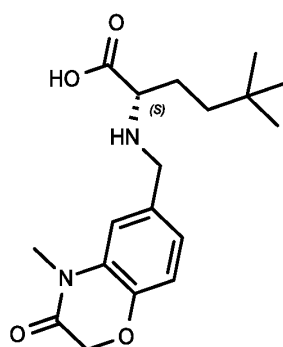


- (2S)-2-([(2,3-dihydro-1H-inden-5-yl)methyl]amino)-5,5-dimethylhexanoic acid:

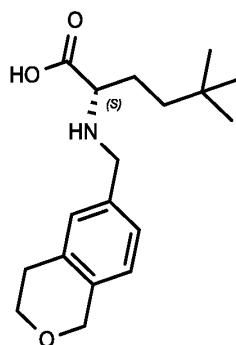
24



- (2S)-5,5-dimethyl-2-[(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)methyl]amino}hexanoic acid:

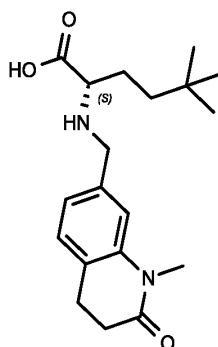


- 5 • (2S)-2-[(3,4-dihydro-1H-2-benzopyran-6-yl)methyl]amino}-5,5-dimethylhexanoic acid:

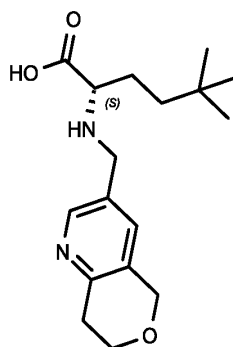


- (2S)-5,5-dimethyl-2-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino}hexanoic acid:

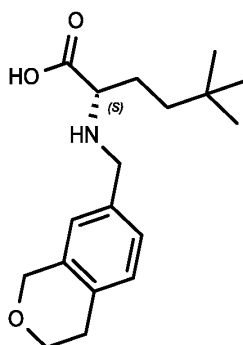
25



- (2S)-5,5-dimethyl-2-[(5H,7H,8H-pyrano[4,3-b]pyridin-3-yl)methyl]amino]hexanoic acid:

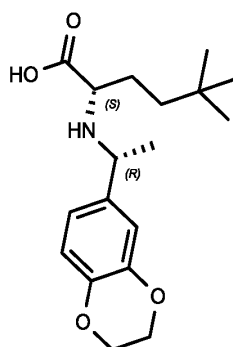


- 5 • (2S)-2-[(3,4-dihydro-1H-2-benzopyran-7-yl)methyl]amino}-5,5-dimethylhexanoic acid:

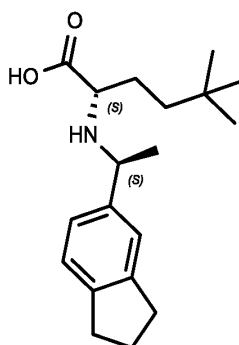


- (2S)-2-[(1R)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-5,5-dimethylhexanoic acid:

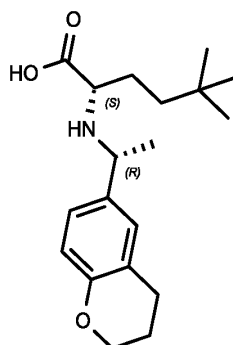
26



- (2S)-2-([(1S)-1-(2,3-dihydro-1H-inden-5-yl)ethyl]amino)-5,5-dimethylhexanoic acid:

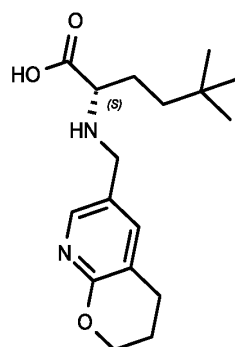


- 5 • (2S)-2-([(1R)-1-(3,4-dihydro-2H-1-benzopyran-6-yl)ethyl]amino)-5,5-dimethylhexanoic acid:

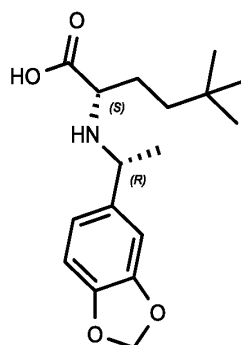


- (2S)-5,5-dimethyl-2-([(2H,3H,4H-pyrano[2,3-b]pyridin-6-yl)methyl]amino)hexanoic acid:

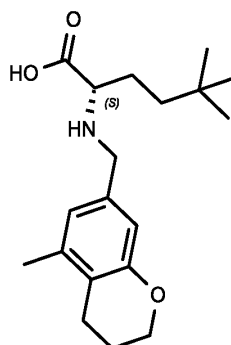
27



- (2S)-2-[(1R)-1-(2H-1,3-benzodioxol-5-yl)ethyl]amino}-5,5-dimethylhexanoic acid:

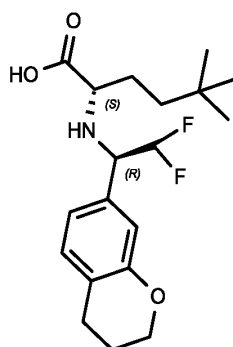


- 5 • (2S)-5,5-dimethyl-2-[(5-methyl-3,4-dihydro-2H-1-benzopyran-7-yl)methyl]amino}hexanoic acid:

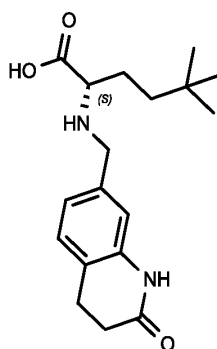


- (2S)-2-[(1R)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)-2,2-difluoroethyl]amino}-5,5-dimethylhexanoic acid:

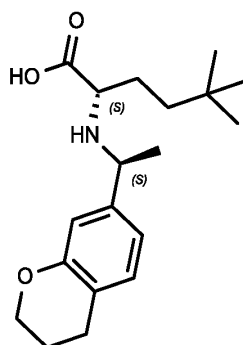
28



- (2S)-5,5-dimethyl-2-([(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino)hexanoic acid:

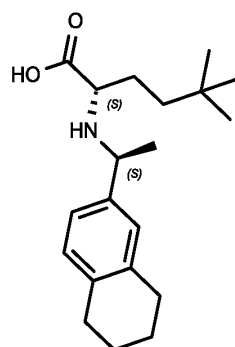


- 5 • (2S)-2-([(1S)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)ethyl]amino)-5,5-dimethylhexanoic acid:

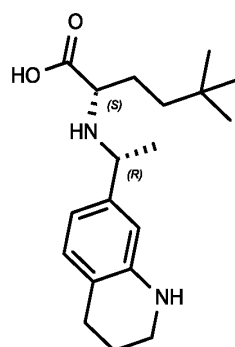


- (2S)-5,5-dimethyl-2-([(1S)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino)hexanoic acid:

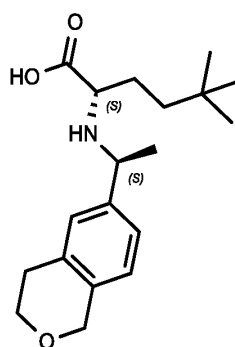
29



- (2S)-5,5-dimethyl-2-[(1R)-1-(1,2,3,4-tetrahydroquinolin-7-yl)ethyl]amino}hexanoic acid:

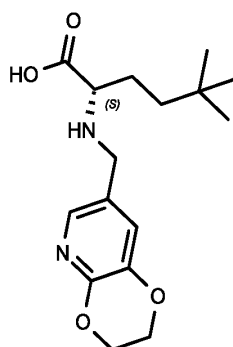


- 5 • (2S)-2-[(1S)-1-(3,4-dihydro-1H-2-benzopyran-6-yl)ethyl]amino}-5,5-dimethylhexanoic acid:

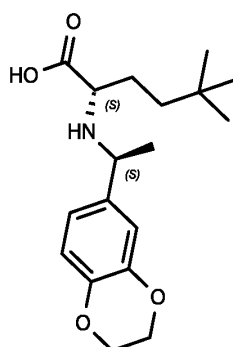


- (2S)-2-[(2H,3H-[1,4]dioxino[2,3-b]pyridin-7-yl)methyl]amino}-5,5-dimethylhexanoic acid:

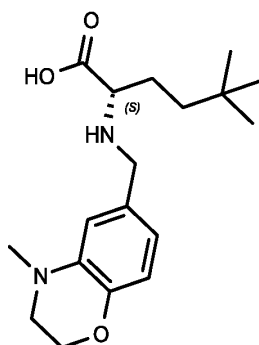
30



- (2S)-2-([(1S)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino)-5,5-dimethylhexanoic acid:

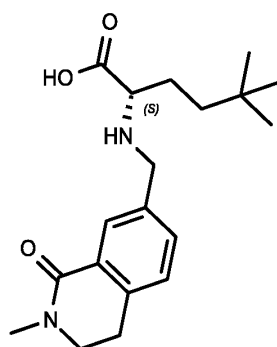


- 5 • (2S)-5,5-dimethyl-2-([(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-6-yl)methyl]amino)hexanoic acid:

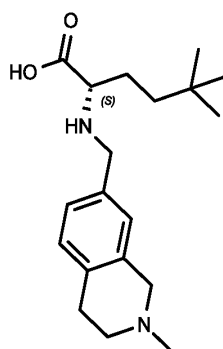


- (2S)-5,5-dimethyl-2-([(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl]amino)hexanoic acid:

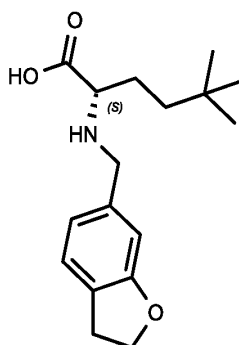
31



- (2S)-5,5-dimethyl-2-([(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl]amino)hexanoic acid:

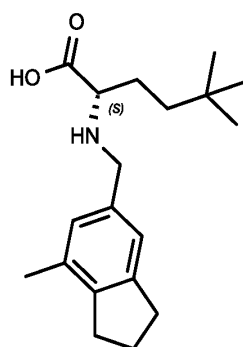


- 5 • (2S)-2-([(2,3-dihydro-1-benzofuran-6-yl)methyl]amino)-5,5-dimethylhexanoic acid:

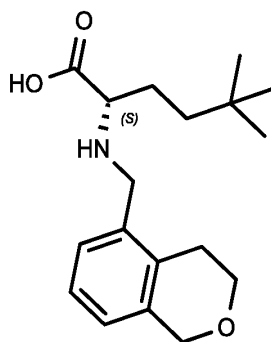


- (2S)-5,5-dimethyl-2-([(7-methyl-2,3-dihydro-1H-inden-5-yl)methyl]amino)hexanoic acid:

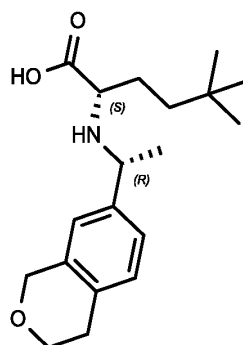
32



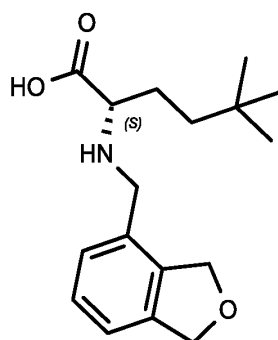
- (2S)-2-([(3,4-dihydro-1H-2-benzopyran-5-yl)methyl]amino)-5,5-dimethylhexanoic acid:



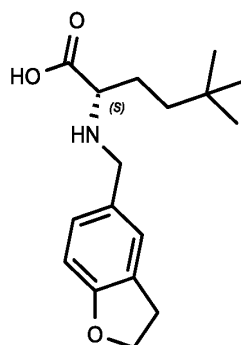
- 5 • (2S)-2-([(1R)-1-(3,4-dihydro-1H-2-benzopyran-7-yl)ethyl]amino)-5,5-dimethylhexanoic acid:



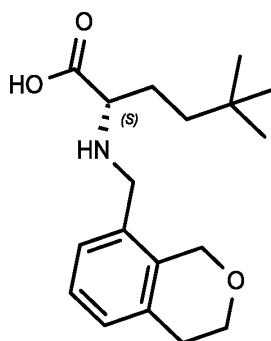
- (2S)-2-([(1,3-dihydro-2-benzofuran-4-yl)methyl]amino)-5,5-dimethylhexanoic acid:



- (2S)-2-[[2,3-dihydro-1-benzofuran-5-yl)methyl]amino]-5,5-dimethylhexanoic acid:

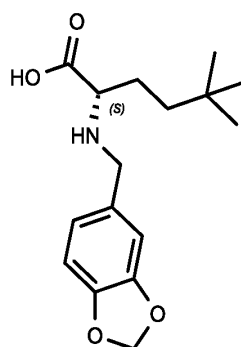


- 5 • (2S)-2-[[3,4-dihydro-1H-2-benzopyran-8-yl)methyl]amino]-5,5-dimethylhexanoic acid:

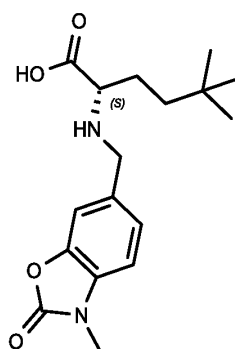


- (2S)-2-[[2H-1,3-benzodioxol-5-yl)methyl]amino]-5,5-dimethylhexanoic acid:

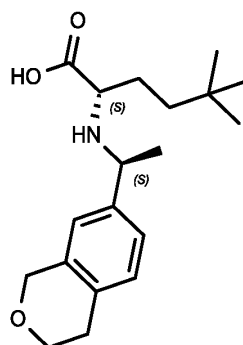
34



- (2S)-5,5-dimethyl-2-([(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)methyl]amino)hexanoic acid:

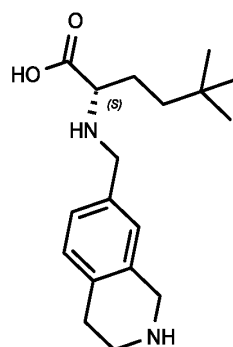


- 5 • (2S)-2-([(1S)-1-(3,4-dihydro-1H-2-benzopyran-7-yl)ethyl]amino)-5,5-dimethylhexanoic acid:

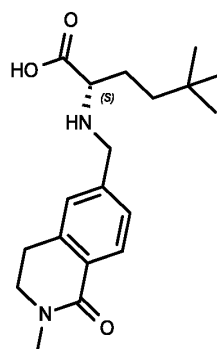


- (2S)-5,5-dimethyl-2-([(1,2,3,4-tetrahydroisoquinolin-7-yl)methyl]amino)hexanoic acid:

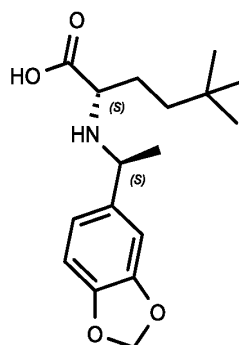
35



- (2S)-5,5-dimethyl-2-([(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]amino)hexanoic acid:

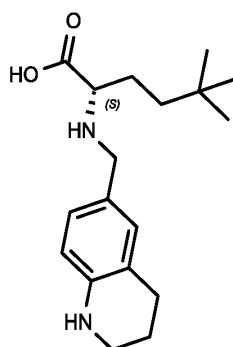


- 5 • (2S)-2-([(1S)-1-(2H-1,3-benzodioxol-5-yl)ethyl]amino)-5,5-dimethylhexanoic acid:

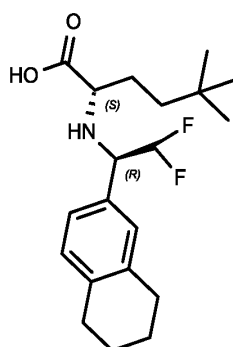


- (2S)-5,5-dimethyl-2-([(1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino)hexanoic acid:

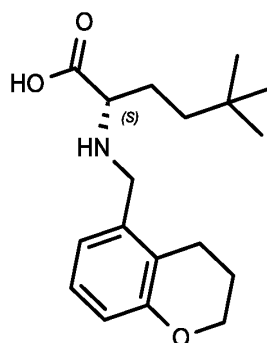
36



- (2S)-2-[[[(1R)-2,2-difluoro-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino]-5,5-dimethylhexanoic acid:

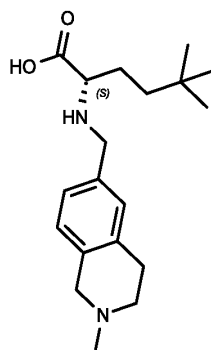


- 5 • (2S)-2-[[[(3,4-dihydro-2H-1-benzopyran-5-yl)methyl]amino]-5,5-dimethylhexanoic acid:

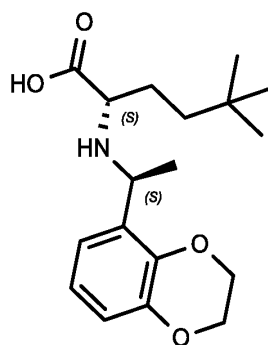


- (2S)-5,5-dimethyl-2-[[[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]amino]hexanoic acid:

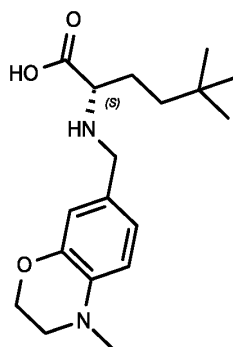
37



- (2S)-2-[[[(1S)-1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]amino]-5,5-dimethylhexanoic acid:

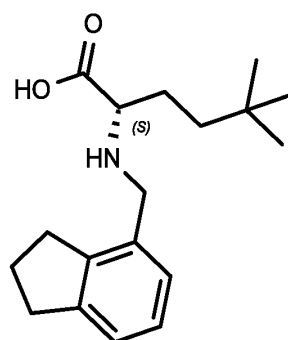


- 5 • (2S)-5,5-dimethyl-2-[[[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)methyl]amino]hexanoic acid:

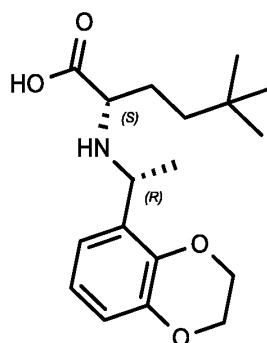


- (2S)-2-[[[(2,3-dihydro-1H-inden-4-yl)methyl]amino]-5,5-dimethylhexanoic acid:

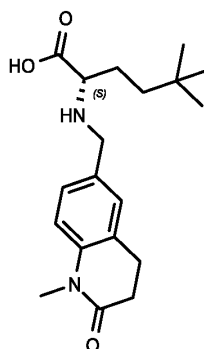
38



- (2S)-2-[[[(1R)-1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]amino]-5,5-dimethylhexanoic acid:

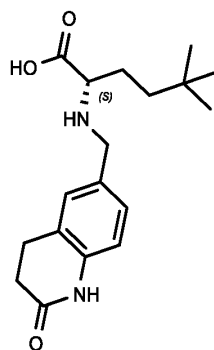


- 5 • (2S)-5,5-dimethyl-2-[[[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino]hexanoic acid:

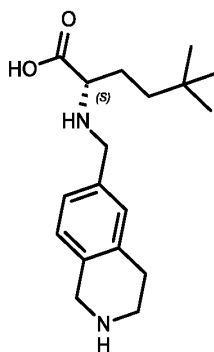


- (2S)-5,5-dimethyl-2-[[[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino]hexanoic acid:

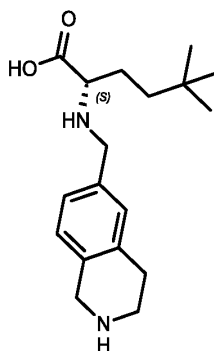
39



- (2S)-5,5-dimethyl-2-[(1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]amino}hexanoic acid:

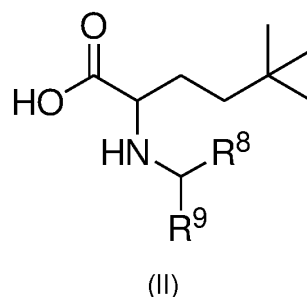


- 5 • (2S)-5,5-dimethyl-2-[(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-7-yl)methyl]amino}hexanoic acid:



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug of the above compounds.

In a second aspect of the invention, there is provided a compound of Formula (II):



- 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug thereof.

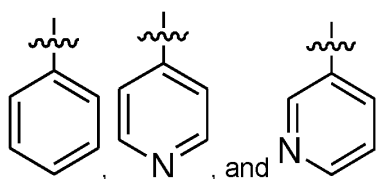
In one embodiment, R^8 is selected from the group consisting of H, C_1 - C_3 alkyl, and C_1 - C_3 haloalkyl, and R^9 is phenyl or pyridine, wherein phenyl and pyridine are independently substituted with one or more substituents selected from the group
 10 consisting of 5-membered heterocycloalkyl, triazolyl, -O-phenyl, and $-NR^{10}R^{11}$.

R^{10} and R^{11} are independently selected from H or C_1 - C_3 alkyl, preferably H or CH_3 , more preferably CH_3 .

Preferably, R^8 is selected from the group consisting of H, CH_3 , CHF_2 , and CF_3 , more preferably H and CH_3 .

- 15 Preferably, R^9 is phenyl substituted with pyrrolidinyl, triazolyl, -O-phenyl, or $-NR^{10}R^{11}$; or R^9 is pyridine substituted with -O-phenyl.

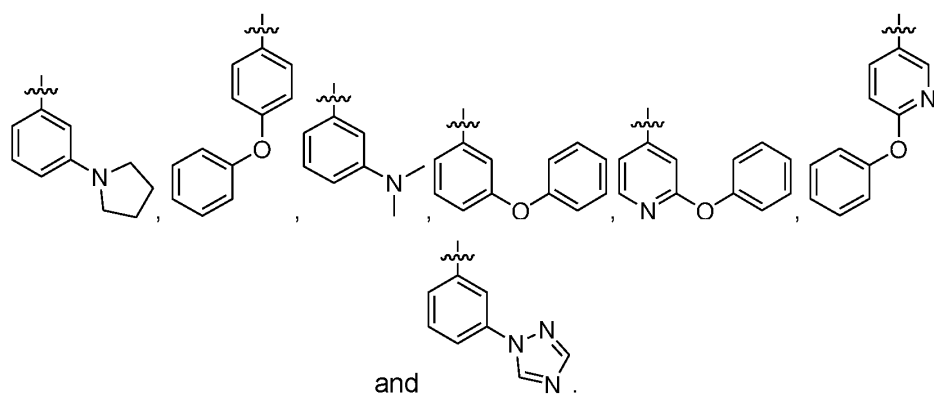
More preferably, R^9 is selected from one of the following groups:



wherein phenyl and pyridine are substituted as defined above.

20

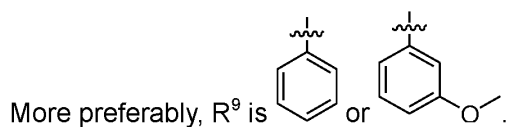
Most preferably, R^9 is selected from one of the following groups:



In an alternative embodiment of the second aspect of the invention, R⁸ is C₁-C₃ hydroxyalkyl and R⁹ is phenyl optionally substituted with C₁-C₃ alkoxy.

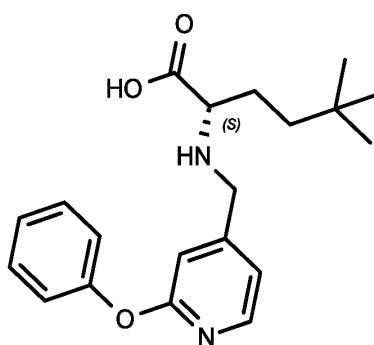
- 5 Preferably, R⁸ is -(C₂H₄)-OH.

Preferably, R⁹ is phenyl optionally substituted with -O-CH₃.



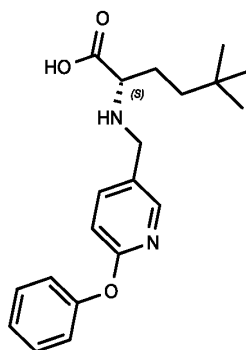
Particular compounds of the second aspect of the invention are those listed below.

- 10 • (2S)-5,5-dimethyl-2-[[(2-phenoxy pyridin-4-yl)methyl]amino]hexanoic acid:

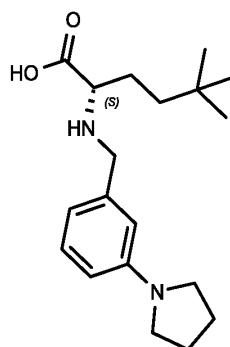


- (2S)-5,5-dimethyl-2-[[[6-phenoxy-pyridin-3-yl)methyl]amino]hexanoic acid:

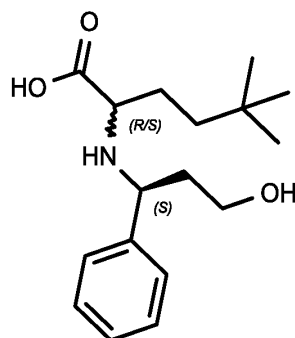
42



- (2S)-5,5-dimethyl-2-({[3-(pyrrolidin-1-yl)phenyl]methyl}amino)hexanoic acid:



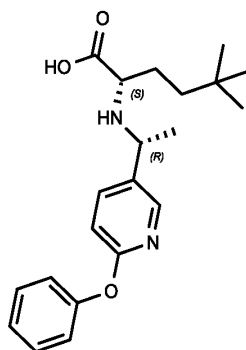
- 2-[[[(1S)-3-hydroxy-1-phenylpropyl]amino]-5,5-dimethylhexanoic acid:



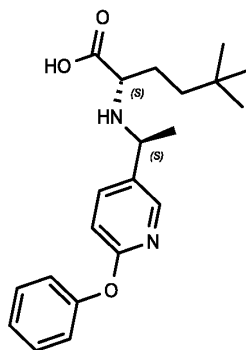
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- (2S)-5,5-dimethyl-2-[[[(1R)-1-(6-phenoxy pyridin-3-yl)ethyl]amino]hexanoic acid:

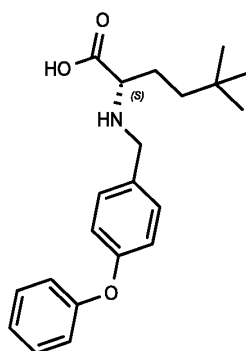
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- (2S)-5,5-dimethyl-2-([(1S)-1-(6-phenoxy-3-pyridyl)ethyl]amino)hexanoic acid:

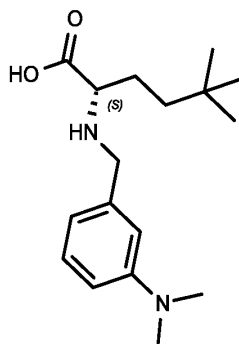


- 5 • (2S)-5,5-dimethyl-2-([(4-phenoxyphenyl)methyl]amino)hexanoic acid:

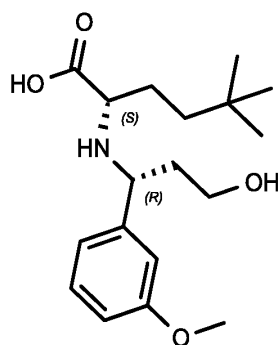


- (2S)-2-([(3-(dimethylamino)phenyl)methyl]amino)-5,5-dimethylhexanoic acid:

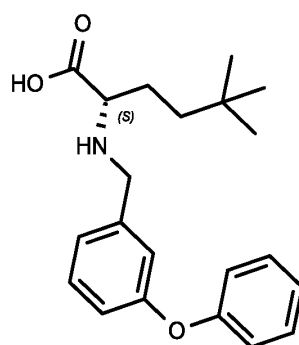
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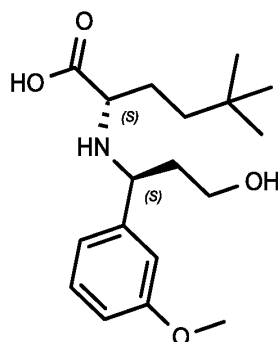
- (2S)-2-[[[(1R)-3-hydroxy-1-(3-methoxyphenyl)propyl]amino]-5,5-dimethylhexanoic acid:



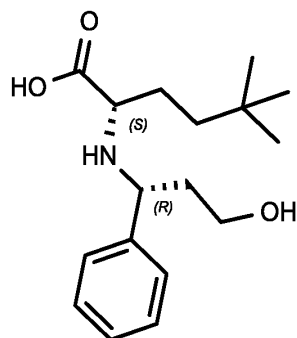
- 5 • (2S)-5,5-dimethyl-2-[[[(3-phenoxyphenyl)methyl]amino]hexanoic acid:



- (2S)-2-[[[(1S)-3-hydroxy-1-(3-methoxyphenyl)propyl]amino]-5,5-dimethylhexanoic acid:

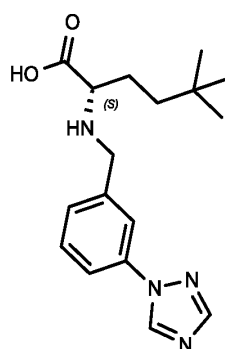


- (2S)-2-[[[(1R)-3-hydroxy-1-phenylpropyl]amino]-5,5-dimethylhexanoic acid:



- (2S)-5,5-dimethyl-2-([3-(1H-1,2,4-triazol-1-yl)phenyl]methyl)amino)hexanoic acid:

46



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug of the above compounds.

According to a third aspect of the invention, there is a pharmaceutical composition
5 comprising a compound according to the invention and a pharmaceutically acceptable carrier, excipient, and/or diluent.

According to a fourth aspect of the invention, there is provided a compound or pharmaceutical composition according to the invention for use in therapy.

According to a fifth aspect of the invention, there is provided a compound or
10 pharmaceutical composition according to the invention for use in the treatment or prevention of a neurodegenerative disorder, a psychiatric disorder, an inflammatory disorder, a cancer, pain, diabetes mellitus, diabetic retinopathy, glaucoma, uveitis, cardiovascular diseases, kidney disease, psoriasis, hereditary eye conditions, hearing loss or diseases characterized by misfolded tau.

15 Preferably, the neurodegenerative disorder is selected from motor neuron diseases, Frontotemporal Lobar Degeneration (FTLD), frontotemporal dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion diseases such as Creutzfeldt-Jakob disease (CJD), acute brain injury, spinal cord injury and stroke, preferably wherein the motor neuron disease is selected from amyotrophic
20 lateral sclerosis (ALS), Primary Lateral Sclerosis, and Progressive Muscular Atrophy.

The neurodegenerative disorder is preferably a neurodegenerative disorder characterised by misfolded TAR DNA binding protein 43 (tdp-43). In other words, the neurodegenerative disease is characterized by truncated tdp-43 and inclusion bodies. Examples of such diseases include amyotrophic lateral sclerosis, 5 Alzheimer's disease, Frontotemporal Lobar Degeneration, and frontotemporal dementia.

Preferably, the psychiatric disorder is selected from bipolar disorder, major depression, post-traumatic stress disorder, and anxiety disorders;

10 Preferably, the inflammatory disorder may be selected from inflammatory diseases and neuroinflammation.

Preferably, the cancer is selected from breast cancer, lung cancer, ovarian cancer, prostate cancer, thyroid cancer, pancreatic cancer, glioblastoma and colorectal cancer.

15 Preferably, the cardiovascular disease is preferably selected from atherosclerosis, cardiomyopathy, heart attack, arrhythmias, heart failure, and ischemic heart disease.

Preferably, the hearing loss is selected from noise-induced hearing loss, ototoxicity induced hearing loss, age-induced hearing loss, idiopathic hearing loss, tinnitus and sudden hearing loss.

20 According to a sixth aspect of the invention, there is provided the use of the compound according to the invention for the manufacture of a medicament for the treatment or prevention of a neurodegenerative disorder, a psychiatric disorder, an inflammatory disorder, a cancer, pain, diabetes mellitus, diabetic retinopathy, glaucoma, uveitis, cardiovascular diseases, kidney disease, psoriasis, hereditary 25 eye conditions, hearing loss or diseases characterized by misfolded tau.

According to a seventh aspect of the invention, there is provided a method for the treatment or prevention of a disease or condition responsive to sortilin modulation

comprising administering a therapeutically effective amount of a compound or pharmaceutical composition according to the invention.

- The compounds of the invention may include isotopically-labelled and/or isotopically-enriched forms of the compounds. The compounds of the invention
- 5 herein may contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}O , ^{17}O , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl .
- 10 The compounds of the invention may be used as such or, where appropriate, as pharmacologically acceptable salts (acid or base addition salts) thereof. The pharmacologically acceptable addition salts mentioned below are meant to comprise the therapeutically active non-toxic acid and base addition salt forms that the compounds are able to form. Compounds that have basic properties can
- 15 be converted to their pharmaceutically acceptable acid addition salts by treating the base form with an appropriate acid. Exemplary acids include inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulphuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propanoic acid, hydroxyacetic acid, lactic acid, pyruvic acid, glycolic acid, maleic acid,
- 20 malonic acid, oxalic acid, benzenesulphonic acid, toluenesulphonic acid, methanesulphonic acid, trifluoroacetic acid, fumaric acid, succinic acid, malic acid, tartaric acid, citric acid, salicylic acid, p-aminosalicylic acid, pamoic acid, benzoic acid, ascorbic acid and the like. Compounds that have acidic properties can be converted to their pharmaceutically acceptable basic addition salts by treating the
- 25 acid form with an appropriate base. Exemplary base addition salt forms are the sodium, potassium, calcium salts, and salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, and amino acids, such as, e.g. arginine and lysine. The term addition salt as used herein also comprises solvates which the compounds and salts thereof are able to form,
- 30 such as, for example, hydrates, alcoholates and the like.

Throughout the present disclosure, a given chemical formula or name shall also encompass all pharmaceutically acceptable salts, solvates, hydrates, N-oxides, and/or prodrug forms thereof. It is to be understood that the compounds of the invention include any and all hydrates and/or solvates of the compound formulas.

5 It is appreciated that certain functional groups, such as the hydroxy, amino, and like groups form complexes and/or coordination compounds with water and/or various solvents, in the various physical forms of the compounds. Accordingly, the above formulas are to be understood to include and represent those various hydrates and/or solvates.

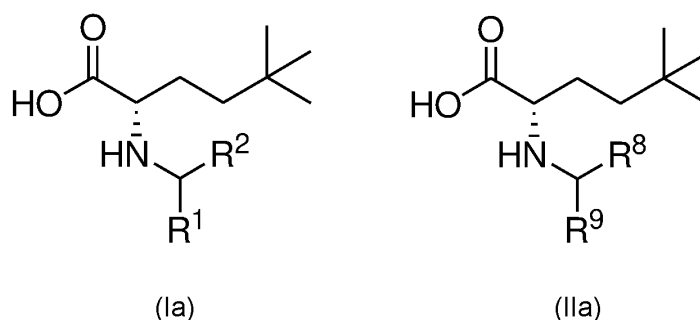
10 Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone - enol
15 pairs, amide - imidic acid pairs, lactam - lactim pairs, amide - imidic acid pairs, enamine - imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by
20 appropriate substitution.

The compounds described herein can be asymmetric (e.g. having one or more stereogenic centres). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active
25 or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis-
30 and trans-geometric isomers of the compounds of the present invention are

described and may be isolated as a mixture of isomers or as separated isomeric forms.

In the case of the compounds which contain an asymmetric carbon atom, the invention relates to the D form, the L form, and D,L mixtures and also, where more than one asymmetric carbon atom is present, to the diastereomeric forms. Those compounds of the invention which contain asymmetric carbon atoms, and which as a rule accrue as racemates, can be separated into the optically active isomers in a known manner, for example using an optically active acid. However, it is also possible to use an optically active starting substance from the outset, with a corresponding optically active or diastereomeric compound then being obtained as the end product.

Preferably, the compounds of Formula (I) and (II) are compounds of Formula (Ia) and (IIa) respectively:



15

The term "prodrugs" refers to compounds that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. A prodrug may be inactive when administered to a subject in need thereof, but is converted in vivo to an active compound of the invention. Prodrugs are typically rapidly transformed in vivo to yield the parent compound of the invention, e.g. by hydrolysis in the blood. The prodrug compound usually offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see Silverman, R. B., The Organic Chemistry of Drug Design and Drug Action, 2nd Ed., Elsevier Academic Press (2004), page 498 to 549). Prodrugs of a compound of the invention may be prepared by modifying functional groups,

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such as a hydroxy, amino or mercapto groups, present in a compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound of the invention. Examples of prodrugs include, but are not limited to, acetate, formate and succinate derivatives of hydroxy functional groups or phenyl carbamate derivatives of amino functional groups.

The compounds of the invention may be sortilin inhibitors, binders, modulators or antagonists. As used herein, the term "sortilin antagonist", "sortilin inhibitor", "sortilin binder" or "sortilin modulator" (used interchangeably) refers to a substance that interferes with, blocks, or otherwise attenuates the effect of, a sortilin protein binding to progranulin, or neurotensin or another extracellular ligand, or a pro-neurotrophin (e.g., pro-NGF, proNT3, pro-BDNF) or preventing the formation of the trimeric complex between sortilin, p75NTR and the pro-neurotrophin. The term "sortilin antagonist" also includes a substance or agent that interferes with the formation of a high affinity trimeric complex. In the latter scenario, it is recognised that a trimeric complex may be formed in that sortilin can bind to p75NTR (but not pro-NGF) and p75NTR can simultaneously bind the NGF domain of pro-NGF. However, the resulting trimeric complex may be of lower affinity for its receptor and as a result have significantly reduced capacity to stimulate apoptosis via the mechanism described above. Skeldal et al. (2012) demonstrated that the apoptotic function of the trimeric complex is abolished when sortilin is devoid in its intracellular domain. The term "sortilin antagonist" also includes a substance or agent that interferes with, blocks, or otherwise attenuates the effect of, a sortilin protein interacting with p75NTR. This interaction may be completely prevented, in which case the trimeric complex is prevented from forming, or only partially prevented, in which case the trimeric complex may be formed but may have reduced biological potency. Skeldal et al showed that complex formation between sortilin and p75NTR relies on contact points in the extracellular domains of the receptors and that the interaction critically depends on an extracellular juxtamembrane 23-amino acid sequence of p75NTR. Thus, the sortilin antagonist may interfere with this 23-amino acid sequence or proximal

sequences in the molecules. "Sortilin antagonists" may act as ligand cellular uptake inhibitors wherein the ligands may be progranulin, neurotensin, BDNF etc.

The compounds of the invention may cross the blood brain barrier and therefore may be particularly useful in the treatment or prevention of diseases of the central nervous system, including neurodegenerative disorders selected from motor neuron diseases, Frontotemporal Lobar Degeneration (FTLD), frontotemporal dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion diseases such as Creutzfeldt-Jakob disease (CJD), acute brain injury, spinal cord injury and stroke; a psychiatric disorder selected from bipolar disorder, major depression, post-traumatic stress disorder, and anxiety disorders; hearing loss selected from noise-induced hearing loss, ototoxicity induced hearing loss, age-induced hearing loss, idiopathic hearing loss, tinnitus and sudden hearing loss; brain tumours, retinopathies, glaucoma, neuroinflammation, chronic pain and diseases characterized by misfolded tau.

The compounds of the invention may have a K_{puu} of more than 0.1, such as between 0.1 and 10, between 0.1 and 5, between 0.1 and 3, between 0.1 and 2, between 0.1 and 1, between 0.1 and 0.8, between 0.1 and 0.6, between 0.1 and 0.5, between 0.1 and 0.4, between 0.1 and 0.3, or between 0.1 and 0.2.

The term "treatment" as used herein may include prophylaxis of the named disorder or condition, or amelioration or elimination of the disorder once it has been established. The term "prevention" refers to prophylaxis of the named disorder or condition.

Methods delineated herein include those wherein the subject is identified as in need of a particular stated treatment. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

In other aspects, the methods herein include those further comprising monitoring subject response to the treatment administrations. Such monitoring may include periodic imaging or sampling of subject tissue, fluids, specimens, cells, proteins,

chemical markers, genetic materials, etc. as markers or indicators of the treatment regimen. In other methods, the subject is pre-screened or identified as in need of such treatment by assessment for a relevant marker or indicator of suitability for such treatment.

- 5 The invention provides a method of monitoring treatment progress. The method includes the step of determining a level of diagnostic marker (Marker) (e.g. any target or cell type delineated herein modulated by a compound herein) or diagnostic measurement (e.g., screen, assay) in a subject suffering from or susceptible to a disorder or symptoms thereof delineated herein, in which the
- 10 subject has been administered a therapeutic amount of a compound herein sufficient to treat the disease or symptoms thereof. The level of Marker determined in the method can be compared to known levels of Marker in either healthy normal controls or in other afflicted patients to establish the subject's disease status. In preferred embodiments, a second level of Marker in the subject
- 15 is determined at a time point later than the determination of the first level, and the two levels are compared to monitor the course of disease or the efficacy of the therapy. In certain preferred embodiments, a pre-treatment level of Marker in the subject is determined prior to beginning treatment according to this invention; this pre-treatment level of Marker can then be compared to the level of Marker in the
- 20 subject after the treatment commences, to determine the efficacy of the treatment.

A level of Marker or Marker activity in a subject may be determined at least once. Comparison of Marker levels, e.g., to another measurement of Marker level obtained previously or subsequently from the same patient, another patient, or a normal subject, may be useful in determining whether therapy according to the

25 invention is having the desired effect, and thereby permitting adjustment of dosage levels as appropriate. Determination of Marker levels may be performed using any suitable sampling/expression assay method known in the art or described herein. Preferably, a tissue or fluid sample is first removed from a subject. Examples of suitable samples include blood, urine, tissue, mouth or cheek cells, and hair

30 samples containing roots. Other suitable samples would be known to the person skilled in the art. Determination of protein levels and/or mRNA levels (e.g., Marker

levels) in the sample can be performed using any suitable technique known in the art, including, but not limited to, enzyme immunoassay, ELISA, radiolabelling/assay techniques, blotting/ chemiluminescence methods, real-time PCR, and the like.

- 5 For clinical use, the compounds disclosed herein are formulated into pharmaceutical compositions (or formulations) for various modes of administration. It will be appreciated that compounds of the invention may be administered together with a physiologically acceptable carrier, excipient, and/or diluent (i.e. one, two, or all three of these). The pharmaceutical compositions
- 10 disclosed herein may be administered by any suitable route, preferably by oral, rectal, nasal, topical (including ophthalmic, buccal and sublingual), sublingual, transdermal, intrathecal, transmucosal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. Other formulations may conveniently be presented in unit dosage form, e.g., tablets and sustained
- 15 release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. Pharmaceutical formulations are usually prepared by mixing the active substance, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutically acceptable carriers, diluents or excipients. Examples of excipients are water, gelatin, gum arabicum, lactose, microcrystalline
- 20 cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such formulations may also contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like. Usually, the amount of active compounds is between
- 25 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and more preferably between 1-50% by weight in preparations for oral administration. The formulations can be further prepared by known methods such as granulation, compression, microencapsulation, spray coating, Etc. The formulations may be prepared by conventional methods in the
- 30 dosage form of tablets, capsules, granules, powders, syrups, suspensions, suppositories or injections. Liquid formulations may be prepared by dissolving or suspending the active substance in water or other suitable vehicles. Tablets and

granules may be coated in a conventional manner. To maintain therapeutically effective plasma concentrations for extended periods of time, compounds disclosed herein may be incorporated into slow-release formulations.

The dose level and frequency of dosage of the specific compound will vary depending on a variety of factors including the potency of the specific compound employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 100 mg per kilo of body weight, administered singly or multiply in doses, e.g. from about 0.01 mg to about 25 mg each. Normally, such a dosage is given orally but parenteral administration may also be chosen.

DEFINITIONS

As used herein, the term "sortilin" may refer to full length sortilin (also referred to as immature sortilin), comprising a signal peptide, a propeptide, a Vps10p domain, a 10CC domain, a transmembrane domain and a large cytoplasmic tail, having an amino acid sequence according to SEQ ID NO: 1 or SEQ ID NO: 2, or it may refer to mature sortilin, comprising a Vps10p domain, a 10CC domain, a transmembrane domain and a large cytoplasmic tail, having an amino acid sequence according to SEQ ID NO: 3, or a naturally occurring fragment, homologue or variant thereof. The term "sortilin" or "sortilin molecule" are used interchangeably herein. It is understood that sortilin is capable of interacting with a pro-neurotrophin molecule to form a sortilin/pro-neurotrophin complex. This sortilin/pro-neurotrophin complex may or may not be capable of interacting with a p75NTR molecule to form a trimeric complex comprising sortilin, pro-neurotrophin and p75NTR. It is understood that this trimeric complex may be responsible for adverse biological responses, such as stimulating apoptosis in retinal and ganglion cells, and controlling growth cone retraction of projecting axons (Jansen et al., 2007; Nykjaer et al., 2004; Santos et al., 2012; Skeldal et al., 2012).

As used herein, the term “pro-neurotrophin” refers to the larger precursors of neurotrophins, which undergo proteolytic cleavage to yield the mature form of the neurotrophin. Neurotrophins are a family of proteins that induce the survival, development and function of neurons, and are commonly referred to as growth factors. Pro-neurotrophins are biologically active and have distinct roles compared to their neurotrophin counterparts, such as induction of apoptosis. Examples of pro-neurotrophins include pro-NGF, pro-BDNF, proNT3 and proNT4. Pro-neurotrophins may also control synaptic plasticity. Whereas mature neurotrophins induce synaptic strength, in their proforms they may weaken synapses.

- 10 “Optional” or “optionally” means that the subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

The term “heteroatom” means O, N, or S.

- 15 The term “(C₁-C_n)alkyl” denotes a straight, branched, cyclic, or partially cyclic alkyl group having from 1 to n carbon atoms, i.e. 1, 2, 3... or n carbon atoms. For the “(C₁-C_n)alkyl” group to comprise a cyclic portion it should be formed of at least three carbon atoms. For parts of the range “(C₁-C_n)alkyl” all subgroups thereof are contemplated. For example, in the range (C₁-C₆)alkyl, all subgroups such as (C₁-C₅)alkyl, (C₁-C₄)alkyl, (C₁-C₃)alkyl, (C₁-C₂)alkyl, (C₁)alkyl, (C₂-C₆)alkyl, (C₂-C₅)alkyl, (C₂-C₄)alkyl, (C₂-C₃)alkyl, (C₂)alkyl, (C₃-C₆)alkyl, (C₃-C₅)alkyl, (C₃-C₄)alkyl, (C₃)alkyl, (C₄-C₆)alkyl, (C₄-C₅)alkyl, (C₄)alkyl, (C₅-C₆)alkyl, (C₆)alkyl. Examples of “C₁-C₆ alkyl” include methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclobutyl, cyclopropylmethyl, branched or cyclic or partially cyclic pentyl and hexyl etc.

- 25 The term “(C₁-C_n) haloalkyl” denotes a C₁-C_n alkyl as described above substituted with at least one halogen atom, which is preferably, F, Cl, Br and I, more preferably F and Cl, and most preferably F.

The term “(C₁-C_n) hydroxyalkyl” denotes a C₁-C_n alkyl as described above substituted with at least one -OH group.

The term "(C₁-C_n)alkoxy" denotes -O-((C₁-C_n)alkyl) in which a (C₁-C_n)alkyl group is as defined above and is attached to the remainder of the compound through an oxygen atom.

When a term denotes a range, for instance "1 to 6 carbon atoms" in the definition of (C₁-C₆)alkyl, each integer is considered to be disclosed, i.e. 1, 2, 3, 4, 5 and 6.

The term "halo" means a halogen atom, and is preferably, F, Cl, Br and I, more preferably F and Cl, and most preferably F.

The term "5-membered heterocycloalkyl" denotes a non-aromatic ring having 5 ring atoms, in which at least one ring atom is a heteroatom. Preferably each heteroatom is independently selected from N, S, or O, more preferably N. Preferably, no more than 2 ring atoms are a heteroatom. More preferably, only one ring atom is a heteroatom.

"An effective amount" refers to an amount of a compound of the invention that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. subject gives an indication of or feels an effect).

As used herein, the terms "administration" or "administering" mean a route of administration for a compound disclosed herein. Exemplary routes of administration include, but are not limited to, oral, intraocular, intravenous, intraperitoneal, intraarterial, and intramuscular. The preferred route of administration can vary depending on various factors, e.g. the components of the pharmaceutical composition comprising a compound disclosed herein, site of the potential or actual disease and severity of disease.

The terms "subject" and "patient" are used herein interchangeably. They refer to a human or another mammal (e.g., mouse, rat, rabbit, dog, cat, cattle, swine, sheep, horse or primate) that can be afflicted with or is susceptible to a disease or disorder but may or may not have the disease or disorder. It is preferred that the subject is human.

Compounds of the invention may be disclosed by the name or chemical structure. If a discrepancy exists between the name of a compound and its associated chemical structure, then the chemical structure prevails.

The invention will now be further illustrated by the following non-limiting examples.

- 5 The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilise the present invention to its fullest extent. All references and publications cited herein are hereby incorporated by reference in their entirety.

10 PREPARATION OF COMPOUNDS OF THE INVENTION

- The compounds of the invention can be prepared according to the following General Synthetic Procedures scheme by methods well known and appreciated in the art. Suitable reaction conditions are well known in the art and appropriate substitutions of solvents and co-reagents are within the common general
- 15 knowledge of the person skilled in the art. Likewise, it will be appreciated by those skilled in the art that synthetic intermediates may be isolated and/or purified by various well-known techniques as needed or desired, and that frequently, it will be possible to use various intermediates directly in subsequent synthetic steps with little or no purification. Furthermore, the skilled person will appreciate that in some
- 20 circumstances, the orders in which moieties are introduced is not critical. The particular order of steps required to produce the compounds of formula (I) or (II) is dependent upon the particular compound being synthesized, the starting compound, and the relative liability of the substituted moieties as is well appreciated by those of ordinary skill in the art. All substituents, unless otherwise
- 25 indicated, are as previously defined, and all reagents are well known and appreciated in the art.

- Suitable starting materials, either optically active as single enantiomers or as racemic mixtures and protected amino acids of general formula AA-1 are either commercially available or may be prepared by a variety of methods. For example,
- 30 as illustrated in the General Synthetic Procedure, **Scheme 1**, the carboxylic acid

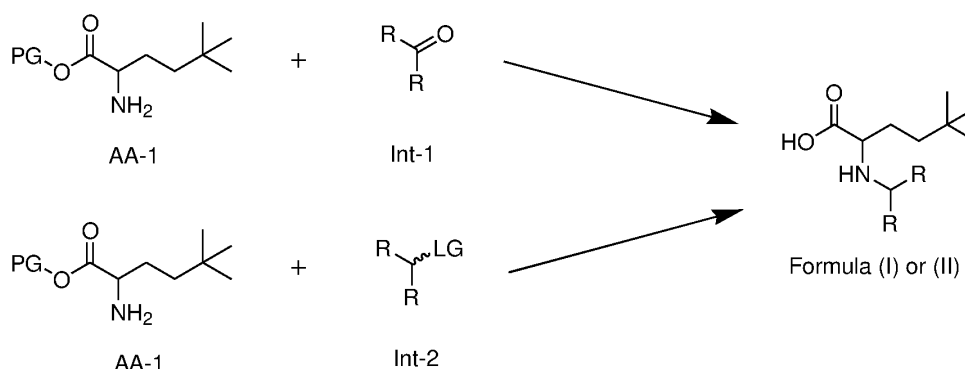
functionality of appropriately substituted amino acids of general formula AA-1, can be used as the free acid, PG = H, or protected as a suitable derivative, for example as a methyl ester. Insertion of the substituent on the primary amine present in AA-1 can be done by a variety of methods, and for the purpose of exemplification,

5 by a reductive amination step involving a suitably substituted carbonyl compound Int-1, aldehyde or ketone and a reductive reagent, as for example but not limited to, sodium triacetoxy borohydride in a suitable solvent mixture like acetic acid and dichloromethane. An alternative method to introduce the substituent on the primary amine present in AA-1, as represented in the general Synthetic

10 Procedures scheme, uses an alkylation step between the suitable protected AA-1 and a reagent of type Int-2. In the later, LG represents a reactive leaving group, as for example, a bromine atom, that can be selectively displaced by the free amine in AA-1, in presence of a suitable base, like, for example, potassium carbonate, in an appropriate solvent like acetonitrile. Alternatively, **Scheme 2**

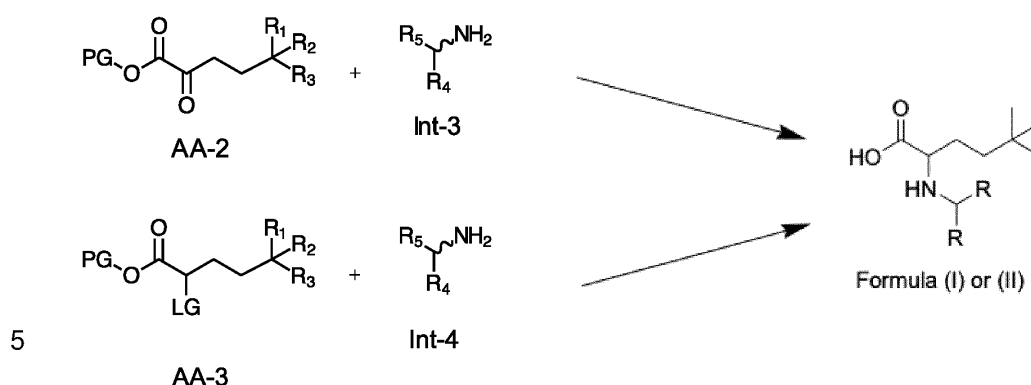
15 exemplifies complementary general synthetic strategies that can be advantageous when, for example, the intermediates of type Int-3 or Int-4 are sterically hindered. Advantageously, intermediates of type AA-2 or AA-3 can be obtained by procedures known, to those skilled in the art, from intermediates of type AA-1, purchased from commercial sources or synthesised.

20 GENERAL SYNTHETIC PROCEDURES



Scheme 1

60



Scheme 2

The compounds of general formula (I) or (II) may be prepared by a variety of procedures, some of which are described below. The products of each step can then be recovered by conventional methods including extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallisation and the like.

Compounds of general formula (I) or (II) may contain one or more stereogenic centres. Those can be introduced from available single enantiomers, optically active, starting materials of the type AA-1. The integrity of the existing stereogenic centre can be confirmed by analytical techniques well known to those skilled in the art like for example chiral support high pressure chromatography. Alternatively, when racemic starting materials are used, it will be appreciated that if desired, single isomer products can be obtained as single enantiomers or as single diastereoisomers, by known techniques like preparative chiral support high pressure chromatography.

The skilled artisan will also appreciate that not all of the substituents in the compounds of formula (I) or (II) will tolerate certain reaction conditions employed to synthesise the compounds. These moieties may be introduced at a convenient point in the synthesis, or may be protected and then deprotected as necessary or desired, as is well known in the art. The skilled artisan will appreciate that the protecting groups may be removed at any convenient point in the synthesis of the compounds of the present invention. Methods for introducing or removing protecting groups used in this invention are well known in the art; see, for example,

Greene and Wuts, Protective Groups in Organic Synthesis, 4th Ed., John Wiley and Sons, New York (2006).

EXAMPLES

5 Abbreviations

- approx: approximately; aq: aqueous; br: broad; *ca.*: *circa*; CDI: 1,1'-Carbonyldiimidazole; d: doublet; DCM: dichloromethane; DIC: *N,N'*-Diisopropylcarbodiimide; dioxane: 1,4-dioxane; DIPEA: diisopropylethylamine; DMF: dimethylformamide; eq.: equivalent; Et₃N: triethylamine; EtOAc: ethyl acetate; EtOH: ethanol; Fmoc: fluorenylmethoxycarbonyl; Boc: *tert*-butoxycarbonyl; h: hours; min: minutes; HATU: 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethyl isouronium hexafluorophosphate(V); HPLC: high performance liquid chromatography; IPA, isopropanol; LC: liquid chromatography; m: multiplet; M: molar, molecular ion; MeCN: acetonitrile; MeOH: methanol; MS: mass spectrometry; NMR: nuclear magnetic resonance; PDA: photodiode array; q: quartet; rt: room temperature (*ca.* 20 °C); R_T: retention time; s: singlet, solid; SPPS: solid phase peptide synthesis. t: triplet; TBAF: tetrabutylammonium fluoride; TBME: *tert*-butyl methyl ether; TFA: trifluoroacetic acid; THF: tetrahydrofuran; UPLC: ultra-performance liquid chromatography; UV: ultraviolet.
- 20 Other abbreviations are intended to convey their generally accepted meaning.

General Experimental Conditions

- All starting materials and solvents were obtained either from commercial sources or prepared according to the literature citation. Reaction mixtures were magnetically stirred, and reactions performed at room temperature (*ca.* 20 °C) unless otherwise indicated.

Column chromatography was performed on an automated flash chromatography system, such as a CombiFlash Rf system, using pre-packed silica (40 µm) cartridges, unless otherwise indicated.

¹H-NMR spectra were recorded at 400 MHz on a Bruker Avance AV-I-400 or on a Bruker Avance AV-II-400 instrument. Chemical shift values are expressed in ppm-values relative to tetramethylsilane unless noted otherwise. The following abbreviations or their combinations are used for multiplicity of NMR signals: br = broad, d = doublet, m = multiplet, q = quartet, quint = quintet, s = singlet and t = triplet.

Analytical Methods

¹H-NMR spectra were recorded at 400 MHz on a Bruker Avance AV-I-400 instrument or on a Bruker Avance AV-II-400 instrument. Chemical shift values are expressed in ppm-values relative to tetramethylsilane unless noted otherwise. The following abbreviations or their combinations are used for multiplicity of NMR signals: br = broad, d = doublet, m = multiplet, q = quartet, quint = quintet, s = singlet and t = triplet.

Method 1: UPLC_AN_BASE, Apparatus: Waters IClass; Bin. Pump: UPIBSM, SM: UPISMFTN with SO; UPCMA, PDA: UPPDATC, 210-320 nm, SQD: ACQ-SQD2 ESI; ELSD: gaspressure 40 psi, drift tube temp: 50°C; column: Waters XSelect CSH C18, 50x2.1mm, 2.5µm, Temp: 25°C, Flow: 0.6 mL/min, Gradient: t₀ = 5% B, t_{2.0min} = 98% B, t_{2.7min} = 98% B, Posttime: 0.3 min, Eluent A: 10mM ammonium bicarbonate in water (pH=9.5), Eluent B: acetonitrile.

Method 2: PREP_ACID-AS4A, Apparatus: Agilent Technologies G6130B Quadrupole; HPLC instrument type: Agilent Technologies 1290 preparative LC; Column: Waters XSelect CSH (C18, 100x30mm, 10µ); Flow: 55 mL/min; Column temp: RT; Eluent A: 0.1% formid acid in water; Eluent B: 100% acetonitrile lin. gradient: t=0 min 20% B, t=2 min 20% B, t=8.5 min 60% B, t=10 min 100% B, t=13 min 100% B; Detection: DAD (220-320 nm); Detection: MSD (ESI pos/neg) mass range: 100 – 1000; fraction collection based on MS and DAD.

Method 3: UPLC_AN_ACID, Apparatus: Waters IClass; Bin. Pump: UPIBSM, SM: UPISMFTN with SO; UPCMA, PDA: UPPDATC, 210-320 nm, SQD: ACQ-SQD2 ESI; ELSD: gaspressure 40 psi, drift tube temp: 50°C; column: Waters XSelect

CSH C18, 50x2.1mm, 2.5µm, Temp: 40°C, Flow: 0.6 mL/min, Gradient: t₀ = 5% B, t_{2.0min} = 98% B, t_{2.7min} = 98% B, Posttime: 0.3 min, Eluent A: 0.1% formic acid in water, Eluent B: 0.1% formic acid in acetonitrile.

Method 4: Apparatus: Agilent Technologies G6130B Quadrupole; HPLC instrument type: Agilent Technologies 1290 preparative LC; Column: Waters XSelect CSH (C18, 100x30mm, 10µ); Flow: 55 ml/min; Column temp: RT; Eluent A: 0.1% formic acid in water; Eluent B: 100% acetonitrile; Detection: DAD (220-320 nm); Detection: MSD (ESI pos/neg) mass range: 100 – 1000; fraction collection based on MS and DAD.

Method 5: Apparatus: ACQ-SQD2; HPLC instrument type: Waters Modular Preparative HPLC System; column: Waters XSelect (C18, 100x30mm, 10µm); flow: 55 ml/min prep pump; column temp: RT; eluent A: 10mM ammonium bicarbonate in water pH=9.5, eluent B: 100% acetonitrile; detection: DAD (220-320 nm); detection: MSD (ESI pos/neg) mass range: 100 – 800; fraction collection based on MS and DAD.

Method 6: Apparatus: Waters IClass; Bin. Pump: UPIBSM, SM: UPISMFTN with SO; UPCMA, PDA: UPPDATC, 210-320 nm, SQD: MS: QDA ESI, pos/neg 100-800; column: Waters XSelect CSH C18, 50x2.1mm, 2.5µm, Temp: 25°C, Flow: 0.6 mL/min, Gradient: t₀ = 5% B, t_{1.3min} = 98% B, t_{1.7min} = 98% B, Posttime: 0.3 min, Eluent A: 10mM ammonium bicarbonate in water (pH=9.5), Eluent B: acetonitrile. MS parameters: Source: ESI; Capillary: 2500 V; Cone: 20 V; Extractor: 3.0 V; RF: 2.5 V; Source Temp.: 150°C; Desolvation Temp.: 600°C; Cone Gas Flow: 80 L/Hr; Desolvation Gas Flow: 1000 L/Hr; Full MS scan: MS range 100-800 (positive and negative mode); scan: 0.4 sec.

Method 7: UPLC_AN_BASE, Instrument: Waters I-Class UPLC, Binary Solvent Manager (BSM), Sample Manager-FTN (SM-FTN) and Sample Organizer (SO), Column Manager (CM-A), PDA 210-320nm, QDa ESI 100-800 (pos) 100-800 (neg), Column: XSelect CSH C18 XP (50x2.1mm 2.5µm) Flow: 0.6 ml/min; Column temp: 25°C, Eluent A: 10mM ammonium bicarbonate in water (pH 9.5),

Eluent B: acetonitrile, Gradient: t=0 min 5% B, t=2 min 98% B, t=2.7 min 98% B, Postrun: 0.3 min.

- Method 8:** MS instrument type: Agilent Technologies G6120AA Quadrupole; HPLC instrument type: Agilent Technologies 1200 preparative LC; Column: 5 Atlantis T3 (C18, 150x19mm, 10µ); Flow: 25 ml/min; Column temp: RT; Eluent A: 0.1% formic acid in water; Eluent B: 100% acetonitrile; copy lin. Gradient from gradient method info here; Detection: DAD (220-320 nm); Detection: MSD (ESI pos/neg) mass range: 100 – 1000; Fraction collection based on MS and DAD.

Method #acid3min – UPLC Acidic Method

- 10 Apparatus: Waters HClass; Binary Solvent Pump, SM-FTN, CMA, PDA, QDa

Column: Waters ACQUITY UPLC® CSH C18, 1.7 µm, 2.1 x 30 mm at 40 °C

Detection: UV at 210-400 nm unless otherwise indicated, MS by electrospray ionisation

Solvents: A: 0.1% Formic in water, B: MeCN

- 15 Gradient:

Time	%A	%B	Flow rate (ml/min)
0.00	98	2	0.77
2.50	0	100	0.77
3.00	0	100	0.77

Method #basic3min – UPLC Basic Method

Apparatus: Waters HClass; Binary Solvent Pump, SM-FTN, CMA, PDA, QDa

Column: Waters ACQUITY UPLC® BEH C18, 1.7 µm, 2.1 x 30 mm at 40 °C

Detection: UV at 210-400 nm unless otherwise indicated, MS by electrospray ionisation

Solvents: A: 0.2% Ammonia in water, B: MeCN

5 Gradient:

Time	%A	%B	Flow rate (ml/min)
0.00	98	2	0.77
2.50	0	100	0.77
3.00	0	100	0.77

Method #acid3minb

Apparatus: Agilent 1260; Quaternary Pump, HiP Sampler, Column Compartment, DAD:, G6150 MSD

10 Column: Waters Cortecs C18, 30 x 2.1 mm, 2.7µm, at 40 °C

Detection: UV at 260nm +/- 90nm unless otherwise indicated, MS by electrospray ionisation

Solvents: A: 0.1% formic acid in water, B: MeCN

Gradient:

Time	%A	%B	Flow rate (ml/min)

0.00	98	2	1.35
2.50	0	100	1.35
3.00	0	100	1.35

Method #basic3minb

Apparatus: Agilent 1260; Quaternary Pump, HiP Sampler, Column Compartment, DAD:, G6150 MSD

- 5 Column: Phenomenex Evo C18, 30 x 2.1 mm, 2.6µm, at 40 °C

Detection: UV at 260nm +/- 90nm unless otherwise indicated, MS by electrospray ionisation

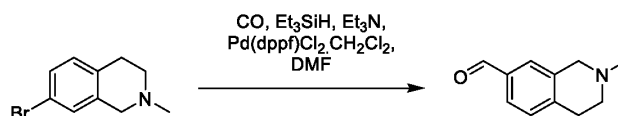
Solvents: A: 0.2% Ammonia in water, B: MeCN

Gradient:

Time	%A	%B	Flow rate (ml/min)
0.00	98	2	1.35
2.50	0	100	1.35
3.00	0	100	1.35

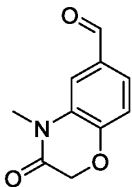
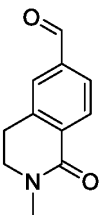
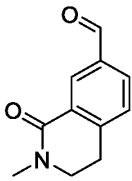
Intermediates

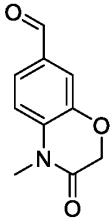
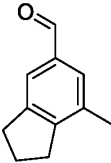
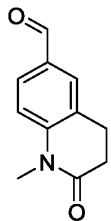
Intermediate 1

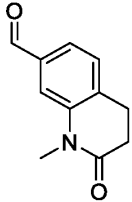
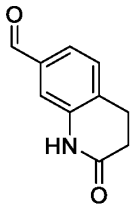
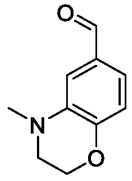


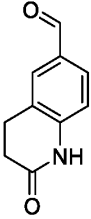
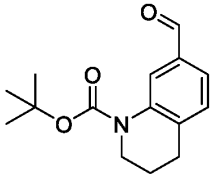
Synthesis of 2-methyl-1,2,3,4-tetrahydroisoquinoline-7-carbaldehyde

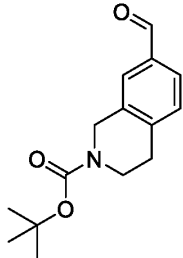
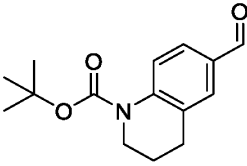
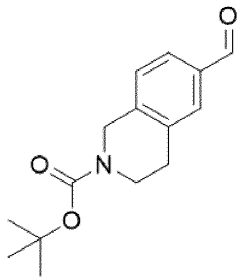
- 5 A solution of 7-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (250 mg, 1 Eq, 1.11 mmol), PdCl₂(dppf).CH₂Cl₂ (80 mg, 0.089 Eq, 98 μmol), Et₃N (336 mg, 0.46 mL, 3 Eq, 3.32 mmol) and triethylsilane (386 mg, 0.53 mL, 3 Eq, 3.32 mmol) in DMF (5 mL) was degassed for 5 min under a stream of N₂ before being sealed. This was then purged with N₂ (x3) before charging with CO (1.5 bar) then the reaction mixture was heated to 90 °C for 2.5 h. The reaction mixture was taken up in EtOAc (40 mL) then washed with sat. aq. NH₄Cl (40 mL), water:brine (2 x 1:1, 40 mL) and brine (40 mL). The organic phase was dried over MgSO₄, filtered and concentrated on to silica (~1 g). The crude product was purified by chromatography on silica gel (12 g cartridge, 0-5% (1% Et₃N/MeOH)/DCM)) to
- 10
- 15 afford 2-methyl-1,2,3,4-tetrahydroisoquinoline-7-carbaldehyde (219 mg, 1.0 mmol, 90 %, 80% Purity) as a brown oil. LCMS (Method #basic3minb, 1.25 min; M+H = 176.2. ¹H NMR (500 MHz, DMSO) δ 9.93 (s, 1H), 7.66 (dd, J = 7.9, 1.7 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 3.58 (s, 2H), 2.91 (t, J = 5.9 Hz, 2H), 2.63 (t, J = 5.9 Hz, 2H), 2.37 (s, 3H).
- 20 The following intermediates were prepared in an analogous manner to intermediate 1, starting from their corresponding aryl bromide.

Int.	Structure	Yield	LCMS	NMR
2		168 mg, (83% yield, 98% Purity)	Method #acid3minb, 1.24 min, M+H = 192.2	¹ H NMR (500 MHz, DMSO) δ 9.93 (s, 1H), 7.63 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 8.0 Hz, 1H), 4.80 (s, 2H), 3.34 (s, 3H).
3		88 mg, (37% yield, 98% Purity)	Method #acid3minb, 1.19 min, M+H = 190.2	¹ H NMR (500 MHz, DMSO) δ 10.05 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.86 (dd, J = 7.8, 1.6 Hz, 1H), 7.83 (d, J = 1.5 Hz, 1H), 3.59 (t, J = 6.7 Hz, 2H), 3.08 (t, J = 6.7 Hz, 2H), 3.05 (s, 3H).
4		69 mg, (29% yield, 98% Purity)	Method #acid3minb, 1.18 min, M+H = 190.2	¹ H NMR (500 MHz, DMSO) δ 10.04 (s, 1H), 8.38 (d, J = 1.8 Hz, 1H), 7.97 (dd, J = 7.8, 1.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 3.59 (t, J = 6.7 Hz, 2H), 3.09 (t, J = 6.7 Hz, 2H), 3.05 (s, 3H).

5		127 mg, (63% yield, 98% Purity)	Method #acid3minb, 1.23 min, M+H = 192.2	1H NMR (500 MHz, DMSO) δ 9.89 (s, 1H), 7.66 (dd, J = 8.3, 1.8 Hz, 1H), 7.46 (d, J = 1.8 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 4.75 (s, 2H), 3.32 (s, 3H).
6		33 mg, (19% yield, 98% Purity)	Method #acid3minb, 1.95 min, M+H = 161.2	1H NMR (400 MHz, DMSO) δ 9.91 (s, 1H), 7.57 (s, 1H), 7.51 (s, 1H), 2.94 (t, J = 7.6 Hz, 2H), 2.86 (t, J = 7.5 Hz, 2H), 2.30 (s, 3H), 2.06 (app. p, J = 7.6 Hz, 2H).
7		111 mg, (69% yield, 98% Purity)	Method #acid3minb, 1.27 min, M+H = 190.2	1H NMR (500 MHz, DMSO) δ 9.90 (s, 1H), 7.83 (dd, J = 8.3, 2.0 Hz, 1H), 7.77 – 7.73 (m, 1H), 7.29 (d, J = 8.4 Hz, 1H), 3.30 (s, 3H), 3.00 – 2.93 (m, 2H), 2.64 – 2.57 (m, 2H).

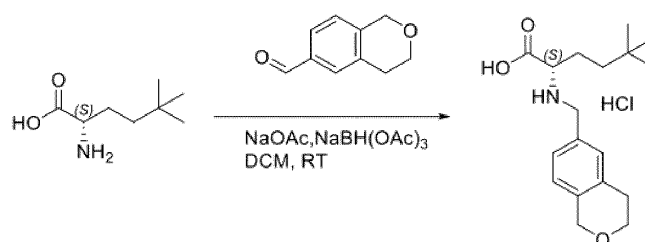
8		73 mg, (43% yield, 98% Purity)	Method #acid3minb, 1.25 min, M+H = 190.2	1H NMR (500 MHz, DMSO) δ 9.99 (s, 1H), 7.59 (dd, J = 7.5, 1.5 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 3.31 (s, 3H), 2.97 (dd, J = 8.5, 6.3 Hz, 2H), 2.62 – 2.55 (m, 2H).
9		36 mg, (23% yield, 98% Purity)	Method #acid3minb, 1.08 min, M+H = 176.0	1H NMR (500 MHz, DMSO) δ 10.34 (s, 1H), 9.90 (s, 1H), 7.49 (dd, J = 7.6, 1.6 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 1.6 Hz, 1H), 2.97 (t, J = 7.6 Hz, 2H).
10		123 mg, (78% yield, 98% Purity)	Method #acid3minb, 1.49 min, M+H = 178.2	1H NMR (500 MHz, DMSO) δ 9.77 (s, 1H), 7.19 (dd, J = 8.0, 1.9 Hz, 1H), 7.14 (d, J = 1.9 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 4.35 – 4.30 (m, 2H), 3.31 – 3.26 (m,

				2H), 2.89 (s, 3H).
11		63 mg, (42% yield, 98% Purity)	Method #acid3minb, 1.03 min, M+H = 176.2	1H NMR (500 MHz, DMSO) δ 10.52 (s, 1H), 9.83 (s, 1H), 7.74 – 7.68 (m, 2H), 7.01 (d, J = 8.0 Hz, 1H), 2.97 (t, J = 7.6 Hz, 2H), 2.55 – 2.51 (m, 2H).
12		280 mg, (66% yield, 98% Purity)	Method #acid3minb, 1.03 min, M- tBu+2H = 206.2	1H NMR (500 MHz, DMSO) δ 9.93 (s, 1H), 8.17 (d, J = 1.5 Hz, 1H), 7.51 (dd, J = 7.7, 1.6 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 3.70 – 3.64 (m, 2H), 2.81 (t, J = 6.5 Hz, 2H), 1.85 (app. p, J = 6.4 Hz, 2H), 1.48 (s, 9H).

13		13 mg, (4.3% yield, 98% Purity)	Method #acid3minb, 1.91 min, M- tBu+2H = 206.2	1H NMR (500 MHz, MeOD) δ 9.95 (s, 1H), 7.77 – 7.70 (m, 2H), 7.39 (d, J = 7.8 Hz, 1H), 4.69 – 4.66 (m, 2H), 3.73 – 3.67 (m, 2H), 2.98 – 2.92 (m, 2H), 1.53 (s, 9H).
14		288 mg, (99% yield, 90% Purity)	Method #acid3minb, 2.03 min, M+H = 262.2	1H NMR (500 MHz, DMSO) δ 9.87 (s, 1H), 7.87 – 7.82 (m, 1H), 7.67 – 7.63 (m, 2H), 3.71 – 3.65 (m, 2H), 2.80 (t, J = 6.4 Hz, 2H), 1.90 – 1.81 (m, 2H), 1.48 (s, 9H).
15		181 mg, (51% yield, 90% Purity)	Method #acid3minb, 1.94 min, M- tBu+2H = 206.2	1H NMR (500 MHz, DMSO) δ 9.96 (s, 1H), 7.74 – 7.68 (m, 2H), 7.41 (d, J = 8.3 Hz, 1H), 4.59 (s, 2H), 3.58 (t, J = 5.9 Hz, 2H), 2.87 (t, J = 5.9 Hz, 2H), 1.43 (s, 9H).

EXAMPLES

Example 1



5

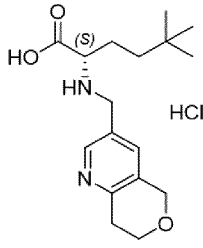
Synthesis of (S)-2-((isochroman-6-ylmethyl)amino)-5,5-dimethylhexanoic acid hydrochloride

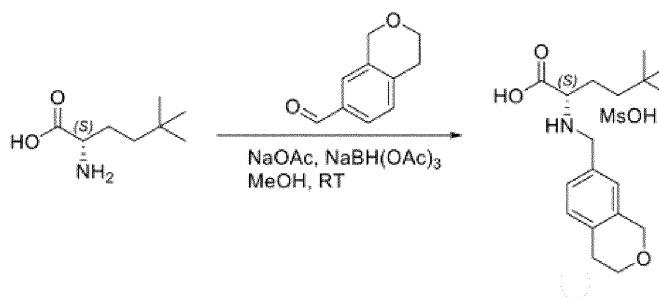
A suspension of isochroman-6-carbaldehyde (102 mg, 0.628 mmol; 1.0 equivalent), (S)-2-amino-5,5-dimethylhexanoic acid (100 mg, 0.63 mmol) and sodium acetate (77 mg, 0.942 mmol; 1.5 equiv.) in dichloromethane (2 mL) was stirred at room temperature for 2 hours before addition of sodium triacetoxyborohydride (266 mg, 1.26 mmol, 2 equiv.). The remaining suspension was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and purified by acidic preparative HPLC (method 2). The product containing fractions were concentrated, reformatted using 1M aqueous HCl and concentrated to afford (S)-2-((isochroman-6-ylmethyl)amino)-5,5-dimethylhexanoic acid hydrochloride (123.7 mg, 0.362 mmol, 57.6 % yield) as a white solid.

LCMS (Method 1, 0.906 min; M+H = 306.5; calcd. 306.2). ¹H-NMR (400 MHz, DMSO) δ 14.02 (br, 1H), 9.37 (s, 2H), 7.31 – 7.27 (m, 2H), 7.10 (d, J = 7.9 Hz, 1H), 4.69 (s, 2H), 4.10 (s, 2H), 3.98 – 3.78 (m, 3H), 2.79 (t, J = 5.7 Hz, 2H), 1.99 – 1.70 (m, 2H), 1.33 (td, J = 13.1, 4.8 Hz, 1H), 1.11 (td, J = 12.9, 4.4 Hz, 1H), 0.86 (s, 9H).

The following example was prepared in an analogous manner to example 1, starting from their corresponding aldehyde.

25

Example	Structure	Yield	LCMS	NMR
2		59.4 mg (55% yield, 94.49% purity)	Method 1, 0.777 min; M+H-HCl- = 307.6; calcd. 307.2	¹ H-NMR (400 MHz, DMSO) δ 10.27 (s, 1H), 9.68 (s, 1H), 8.83 (d, 1H), 8.25 (s, 1H), 4.82 (s, 2H), 4.31 (q, 2H), 4.03 (t, J = 5.7 Hz, 3H), 3.13 (d, J = 11.4 Hz, 2H), 2.03 – 1.84 (m, 2H), 1.41 – 1.30 (m, 1H), 1.18 – 1.06 (m, 1H), 0.87 (s, 9H).

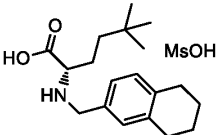
Example 3**Synthesis of (S)-2-((isochroman-7-ylmethyl)amino)-5,5-dimethylhexanoic acid mesylate salt**

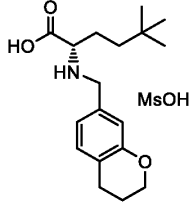
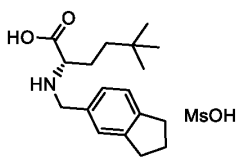
Isochromane-7-carbaldehyde isochromane-7-carbaldehyde (2.26 g, 13.93 mmol; 1.0 equivalent) was added to a mixture of (S)-2-amino-5,5-dimethylhexanoic acid (2.219 g, 13.93 mmol) and sodium acetate sodium acetate (1.715 g, 20.90 mmol; 1.5 equiv.) in Methanol (20 mL). The mixture was stirred at room temperature for 2 hours before addition of sodium triacetoxyborohydride (6.61 g, 31.2 mmol; 2.0 equivalents). The mixture was stirred at room temperature for 16 hours. The product precipitated and was collected by filtration. The residue was washed with Methanol (5 mL) to afford (S)-2-((isochroman-7-ylmethyl)amino)-5,5-

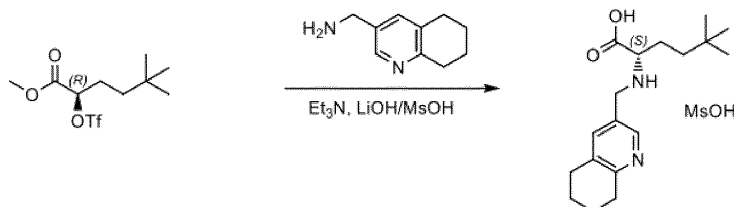
dimethylhexanoic acid (1.42 g, 4.65 mmol, 33 % yield). The mother liquor was concentrated in vacuo. The residue was taken up in EtOAc and washed with water (2x) and brine. The product crashed out of the organic layer and was collected by filtration. The residue was washed with a small amount of EtOAc and dried in vacuo to afford (S)-2-((isochroman-7-ylmethyl)amino)-5,5-dimethylhexanoic acid (1.04 g, 3.41 mmol, 24 % yield). (S)-2-((isochroman-7-ylmethyl)amino)-5,5-dimethylhexanoic acid (1.37 g, 4.48 mmol) was taken up in methanesulfonic acid (0.1M in MeCN) (44.8 ml, 4.48 mmol; 1 equiv.). Water 50 mL was added and the mixture was stirred at 40°C until the product was completely solubilized. The solution was lyophilized to afford (S)-2-((isochroman-7-ylmethyl)amino)-5,5-dimethylhexanoic acid compound **7** with methanesulfonic acid (1.638 g, 4.08 mmol, 29 % yield).

LCMS (Method 1, 0.902 min; M+H = 306.1; calcd. 306.2). ¹H-NMR (400 MHz, DMSO) δ 10.03 (br, 2H), 7.25 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.13 (s, 1H), 4.68 (s, 2H), 4.11 – 3.99 (m, 2H), 3.88 (t, J = 5.7 Hz, 2H), 3.75 – 3.67 (m, 1H), 2.79 (t, J = 5.8 Hz, 2H), 2.30 (s, 3H), 1.86 – 1.67 (m, 2H), 1.30 (td, J = 12.9, 4.9 Hz, 1H), 1.13 (td, J = 12.7, 4.7 Hz, 1H), 0.85 (s, 9H).

The following examples were prepared in an analogous manner to Example 3, starting from their corresponding aldehyde.

Example	Structure	Yield	LCMS	NMR
4		1.18 g (19%, 99.75% purity)	Method 1, 1.253 min; M+H = 318.6; calcd. 318.2)	¹ H-NMR (400 MHz, DMSO) δ 14.01 (br, 1H), 9.28 – 9.00 (m, 2H), 7.21 – 7.15 (m, 2H), 7.15 – 7.06 (m, 1H), 4.08 (s, 2H), 3.89 (s, 1H), 2.72 (d, J = 5.8 Hz, 4H), 2.30 (s, 3H), 1.86 (s, 2H), 1.74 (p, J = 3.2 Hz, 4H), 1.32 (td, J = 13.1, 4.8 Hz, 1H), 1.12 (dt, J = 13.1, 6.5 Hz,

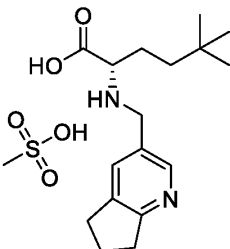
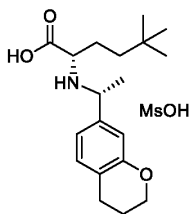
				1H), 0.86 (s, 10H).
5		3.94 g (52% yield, 97.22% purity)	Method 1, 1.015 min; M+H = 306.6; calcd. 306.2)	¹ H-NMR (400 MHz, DMSO) δ 7.08 (d, <i>J</i> = 7.7 Hz, 1H), 6.87 (d, <i>J</i> = 7.6 Hz, 1H), 6.85 (s, 1H), 4.13 (t, <i>J</i> = 5.1 Hz, 2H), 3.97 (q, <i>J</i> = 13.2 Hz, 2H), 3.58 (s, 1H), 2.73 (t, <i>J</i> = 6.5 Hz, 2H), 2.30 (s, 3H), 1.97 – 1.87 (m, 2H), 1.74 (d, <i>J</i> = 17.3 Hz, 2H), 1.28 (dt, <i>J</i> = 13.5, 7.2 Hz, 1H), 1.22 – 1.06 (m, 1H), 0.84 (s, 9H).
6		3.67 g (50%, 94.65 % purity)	Method 1, 1.118 min; M+H = 290.6; calcd. 290.2)	¹ H-NMR (400 MHz, DMSO) δ 10.05 (br, 2H), 7.33 (s, 1H), 7.27 (d, <i>J</i> = 7.6 Hz, 1H), 7.21 (d, <i>J</i> = 7.7 Hz, 1H), 4.13 – 4.01 (m, 2H), 3.74 (t, <i>J</i> = 5.9 Hz, 1H), 2.86 (t, <i>J</i> = 7.4 Hz, 4H), 2.31 (s, 3H), 2.03 (p, <i>J</i> = 7.5 Hz, 2H), 1.87 – 1.68 (m, 2H), 1.31 (td, <i>J</i> = 13.0, 4.9 Hz, 1H), 1.13 (td, <i>J</i> = 12.8, 4.6 Hz, 1H), 0.85 (s, 9H).

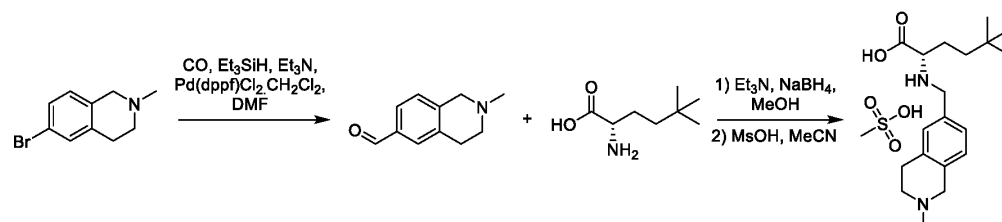
Example 7

Synthesis of (S)-5,5-dimethyl-2-(((5,6,7,8-tetrahydroquinolin-3-yl)methyl)amino)hexanoic acid-methanesulfonic acid

- To a solution of (5,6,7,8-tetrahydroquinolin-3-yl)methanamine dihydrochloride (77 mg, 0.326 mmol, 1.0 equiv.) in dichloromethane (0.9 mL) with triethylamine (148 μ l, 1.061 mmol, 3.25 equiv.) was added a solution of methyl (R)-5,5-dimethyl-2-(((trifluoromethyl)sulfonyl)oxy)hexanoate (100 mg, 0.326 mmol, 1.0 equiv.) in DCM (0.9 mL). The reaction mixture was stirred at room temperature for 3 hours. The solvents were evaporated via nitrogen blow-drying. The crude was redissolved in acetonitrile: water (2 mL, 1:1). Lithium hydroxide (68.5 mg, 1.632 mmol, 5.0 equiv.) was added and the mixture was stirred for 16 hours. The mixture was purified by acidic preparative T3 HPLC (Method 8) to afford (S)-5,5-dimethyl-2-(((R)-1-(5,6,7,8-tetrahydronaphtalen-2-yl)ethyl)amino)hexanoic acid (12.4 mg, 0.039 mmol, 17 % yield). The product was dissolved in acetonitrile (1.1 ml) and methanesulfonic acid (1.0 equiv.) was added. The mixture was lyophilized to afford (S)-5,5-dimethyl-2-(((5,6,7,8-tetrahydroquinolin-3-yl)methyl)amino)hexanoic acid compound with methanesulfonic acid (13.1 mg, 0.033 mmol, 10.02% yield).
- LCMS (Method 7, 0.900 min; $M+H-MsO^- = 305.2$; calcd. 305.2). 1H -NMR (400 MHz, DMSO) δ 8.35 (s, 1H), 7.58 (s, 1H), 4.10 (s, 2H), 2.86 – 2.72 (m, 4H), 2.29 (s, 3H), 1.88 – 1.71 (m, 6H), 1.37 – 1.24 (m, 1H), 1.18 – 1.09 (m, 1H), 0.86 (s, 9H).

- The following example can be prepared in an analogous manner to example 7, starting from the corresponding amine.

Example	Structure	Yield	LCMS	NMR
8		32 mg, (13% yield, 95% purity)	Method #basic3min, 0.77 min, M+H = 291.4	¹ H NMR (500 MHz, DMSO) δ 14.12 (br.s, 1H), 9.38 – 8.98 (m, 2H), 8.37 (s, 1H), 7.73 (s, 1H), 4.17 (s, 2H), 4.04 – 3.93 (m, 1H), 2.93 (app.t, J = 7.6 Hz, 4H), 2.29 (s, 3H), 2.09 (p, J = 7.6 Hz, 2H), 1.94 – 1.71 (m, 2H), 1.32 (app.td, J = 13.1, 4.7 Hz, 1H), 1.15 – 1.07 (m, 1H), 0.86 (s, 9H).
9		33.3 mg (24% yield, 94.53% purity)	LCMS (Method 7, 1.059 min; M+H-MsO- = 320.2; calcd. 320.2)	¹ H-NMR (400 MHz, DMSO) δ 9.17 (s, 1H), 7.14 – 7.08 (m, 1H), 6.99 – 6.89 (m, 2H), 4.34 (d, J = 6.7 Hz, 1H), 4.18 – 4.10 (m, 2H), 3.60 – 3.51 (m, 1H), 2.74 (t, J = 6.4 Hz, 1H), 2.33 (s, 3H), 1.96 – 1.79 (m, 3H), 1.77 – 1.64 (m, 1H), 1.54 (d, J = 6.6 Hz, 2H), 1.33 – 1.20 (m, 1H), 1.01 (td, J = 13.0, 4.1 Hz, 1H), 0.90 – 0.79 (m, 9H).

Example 10

Synthesis of (S)-5,5-dimethyl-2-(((2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)amino)hexanoic acid, Mesylic acid

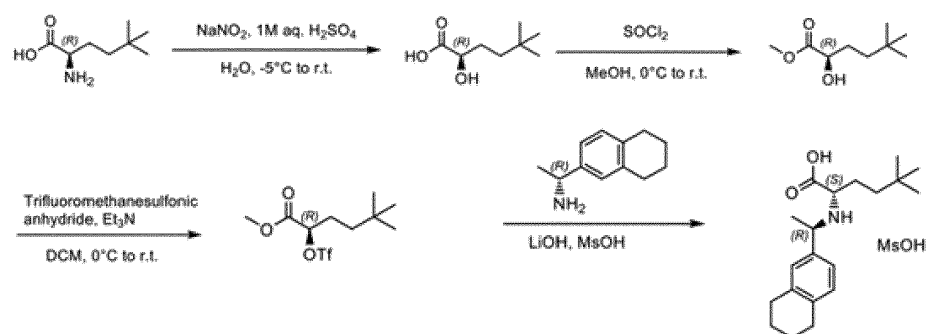
- 5 A solution of 6-bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline (129 mg, 1 Eq, 570 μ mol), triethylamine (173 mg, 239 μ L, 3 Eq, 1.71 mmol), triethylsilane (199 mg, 273 μ L, 3 Eq, 1.71 mmol) and $\text{PdCl}_2(\text{dppf})\text{-CH}_2\text{Cl}_2$ (30 mg, 0.064 Eq, 37 μ mol) in DMF (3.5 mL) was degassed for 5 min under a stream of N_2 before being sealed. This was then purged with N_2 (x3) before charging with CO (1.5 bar) then
- 10 the reaction mixture was heated to 90 $^\circ\text{C}$ for 6 hours. The reaction mixture was taken up in EtOAc (30 mL) then washed with sat. aq. NH_4Cl (20 mL), water:brine (2 x 1:1, 20 mL) and brine (20 mL). The organic phase was dried over MgSO_4 , filtered and concentrated on to silica (~1 g). The crude product was purified by chromatography on silica gel (12 g cartridge, 0-5% (1% Et_3N in MeOH)/DCM) to
- 15 afford 2-methyl-1,2,3,4-tetrahydroisoquinoline-6-carbaldehyde (54 mg, 0.30 mmol, 52 %, 96% Purity) as a brown gum.

- A suspension of (S)-2-amino-5,5-dimethylhexanoic acid (49 mg, 1 Eq, 0.31 mmol) and 2-methyl-1,2,3,4-tetrahydroisoquinoline-6-carbaldehyde (54 mg, 1 Eq, 0.31 mmol) and triethylamine (31 mg, 43 μ L, 1 Eq, 0.31 mmol) in MeOH (5.0
- 20 mL) were stirred for 2 h at 40 $^\circ\text{C}$ to achieve a solution. The mixture was cooled to 0 $^\circ\text{C}$ before sodium borohydride (12 mg, 1 Eq, 0.31 mmol) was added and stirring continued at rt for 1 hour. AcOH (0.1 mL) was added and the reaction mixture was concentrated on to celite (~1 g). The crude product was purified by chromatography on RP Flash C18 (12 g cartridge, 10-50% (0.1 % Formic acid in
- 25 MeCN)/(0.1% Formic Acid in Water)). The isolated fractions were taken up in 2 M NaOH (0.5 mL) and the crude product was repurified by chromatography on RP

Flash C18 (12 g cartridge, 15-50% MeCN/10 mM Ammonium Bicarbonate) to afford the freebase. The freebase was treated with MeOH (1 mL) and 0.1 M MsOH in MeCN (1 equiv) was added before concentrating to dryness to afford (S)-5,5-dimethyl-2-(((2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)amino)hexanoic acid, Mesylic acid (19 mg, 39 μ mol, 13 %, 85% Purity) as a colourless solid.

UPLC (Method #basic3min, 0.72 min; M+H = 319.3. ^1H NMR (500 MHz, DMSO) δ 7.03 – 6.98 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 3.61 – 3.55 (m, 1H), 3.44 – 3.36 (m, 3H), 3.19 – 3.13 (m, 1H), 2.77 (t, J = 6.0 Hz, 2H), 2.59 – 2.52 (m, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 1.46 – 1.11 (m, 4H), 0.81 (s, 9H), 3 x exchangeable Hs not observed.

Example 11



Synthesis of (R)-2-hydroxy-5,5-dimethylhexanoic acid

1M aq. sulfuric acid (226 mL, 226 mmol, 3.0 equiv.) was added to (R)-2-amino-5,5-dimethylhexanoic acid (12 g, 75 mmol, 1.0 equiv.) in water (220 ml). The mixture was cooled to -5°C and a solution of sodium nitrite (31.2 g, 452 mmol, 6.0 equiv.) in Water (220 ml) was added dropwise, keeping the temperature below 0°C. After addition, the mixture was allowed to warm to room temperature and stirred for 16 hours.

The mixture was extracted with Et₂O (4 x 200 mL) and the combined organics were washed with brine (300 mL), dried over Na₂SO₄, filtered and

concentrated *in vacuo* to afford (*R*)-2-hydroxy-5,5-dimethylhexanoic acid (8.98 g, 56.1 mmol, 74.4 % yield) as a yellow solid. ¹H-NMR (400 MHz, CDCl₃) δ 4.28 (dd, J = 7.2, 4.2 Hz, 1H), 1.92 – 1.80 (m, 1H), 1.75 – 1.62 (m, 1H), 1.41 – 1.27 (m, 2H), 0.90 (s, 9H).

5 **Synthesis of methyl (*R*)-2-hydroxy-5,5-dimethylhexanoate**

SOCl₂ (12 ml, 164 mmol, 2.93 equiv.) was added to (*R*)-2-hydroxy-5,5-dimethylhexanoic acid (8.98 g, 56.1 mmol, 1 equiv.) in Methanol (120 ml) at 0°C. After addition, the mixture was allowed to warm to room temperature and stirred for 16 hours. The mixture was alkalized to pH 9 by addition of sat. aq. NaHCO₃ and extracted with Et₂O (2 x 400 mL). Combined organics were dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford methyl (*R*)-2-hydroxy-5,5-dimethylhexanoate (10.01 g, 55.0 mmol, 98 % yield) as yellow oil. Contains 4.2% (w/w) MeOH. ¹H-NMR (400 MHz, CDCl₃) δ 4.18 (dd, J = 7.2, 4.2 Hz, 1H), 3.80 (s, 3H), 1.84 – 1.72 (m, 1H), 1.67 – 1.52 (m, 1H), 1.37 – 1.21 (m, 2H), 0.89 (s, 9H).

Synthesis of methyl (*R*)-5,5-dimethyl-2-(((trifluoromethyl)sulfonyl)oxy)hexanoate

Trifluoromethanesulfonic anhydride (4.65 mL, 27.5 mmol, 1.10 equiv.) was added dropwise to a solution of methyl (*R*)-2-hydroxy-5,5-dimethylhexanoate (4.36 g, 25.02 mmol, 1.0 equiv.) and triethylamine (4.19 mL, 30.0 mmol, 1.2 equiv.) in Dichloromethane (100 mL) at 0°C. After addition, the mixture was allowed to warm to room temperature and stirred for 16 hours. Water (100 mL) was added, and the mixture was extracted with EtOAc (2 x 250 mL). The combined organics were washed with brine (250 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford methyl (*R*)-5,5-dimethyl-2-(((trifluoromethyl)sulfonyl)oxy)hexanoate (7.14 g, 23.31 mmol, 49 % corrected yield) as a dark brown oil. ¹H-NMR (400 MHz, CDCl₃) δ 5.12 (dd, J = 6.9, 5.0 Hz, 1H), 3.85 (s, 3H), 2.05 – 1.90 (m, 2H), 1.36 – 1.24 (m, 2H), 0.90 (s, 9H).

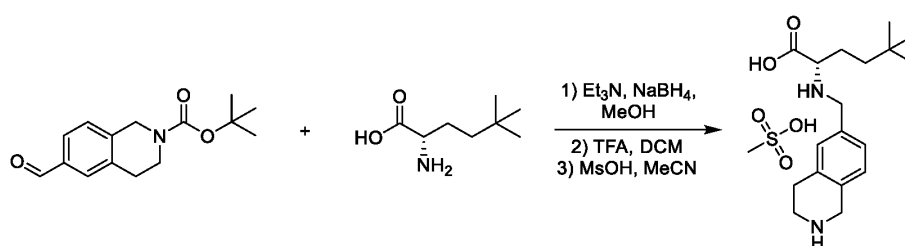
Synthesis of (S)-5,5-dimethyl-2-(((R)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl)amino)hexanoic acid methanesulfonic acid

Methyl (R)-5,5-dimethyl-2-(((trifluoromethyl)sulfonyl)oxy)hexanoate (70 mg, 0.229 mmol, 1.0 equivalent) in dichloromethane (1 mL) was added dropwise to a solution of (R)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-amine (40.1 mg, 0.229 mmol, 1.0 equivalent) in dichloromethane (1 mL). The dichloromethane was removed and the residue was taken up in acetonitrile : water (2 mL, 1:1). Lithium hydroxide (27.4 mg, 1.143 mmol, 5.0 equiv.) was added and the mixture was stirred for 16 hours. The mixture was submitted for acidic preparative HPLC (Method 2) to afford (S)-5,5-dimethyl-2-(((R)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl)amino)hexanoic acid (12.4 mg, 0.039 mmol, 17 % yield). The product was dissolved in acetonitrile (1.1 ml) and methanesulfonic acid (0.1M in acetonitrile) (390 µl, 0.039 mmol, 0.171 equivalent) was added. The mixture was lyophilized to afford (S)-5,5-dimethyl-2-(((R)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl)amino)hexanoic acid-methanesulfonic acid (20.5 mg, 0.050 mmol, 21.7% yield).

LCMS (Method 1, 1.239 min; $M+H-MsO^- = 318.5$; calcd. 318.4). 1H -NMR (400 MHz, DMSO) δ 7.18 (d, $J = 7.8$ Hz, 2H), 7.10 (d, $J = 7.7$ Hz, 1H), 4.26 (d, $J = 6.9$ Hz, 1H), 3.54 – 3.40 (m, 2H), 2.71 (d, $J = 5.7$ Hz, 4H), 2.30 (s, 3H), 1.74 (h, $J = 3.8$ Hz, 4H), 1.52 (d, $J = 6.7$ Hz, 3H), 1.27 (td, $J = 13.0, 4.7$ Hz, 1H), 1.03 (td, $J = 12.8, 3.9$ Hz, 1H), 0.85 (s, 9H).

The following examples can be prepared in an analogous manner to example 11, starting from the corresponding enantiomeric secondary amine.

Example	Structure
12	
13	
14	

Example 15

Synthesis of (S)-2-((3,4-dimethylbenzyl)amino)-5,5-dimethylhexanoic acid, Mesylic acid

5

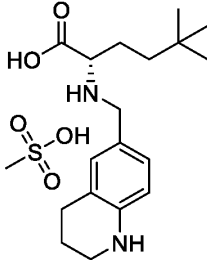
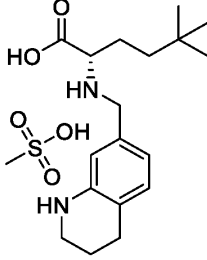
A suspension of (S)-2-amino-5,5-dimethylhexanoic acid (61 mg, 1.0 Eq, 0.38 mmol), tert-butyl 6-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (100 mg, 1 Eq, 383 μmol) and Et_3N (40 mg, 55 μL , 1.0 Eq, 0.39 mmol) in MeOH (3 mL)

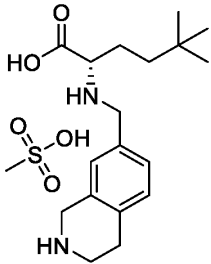
was heated at 40 °C for 2 hours before being cooled with an ice bath and treated with NaBH₄ (15 mg, 1.0 Eq, 0.40 mmol). The mixture was allowed to warm to rt before concentrating to dryness and suspending in water (5 mL). Acetic acid (42 mg, 40 µL, 1.8 Eq, 0.70 mmol) was added before filtering. The material was suspended in water (10 mL) and acetone (2 mL) before heating at 60 °C for 30 min. After cooling to rt, the Boc protected freebase (112 mg, 0.28 mmol, 74% yield) was collected by filtration.

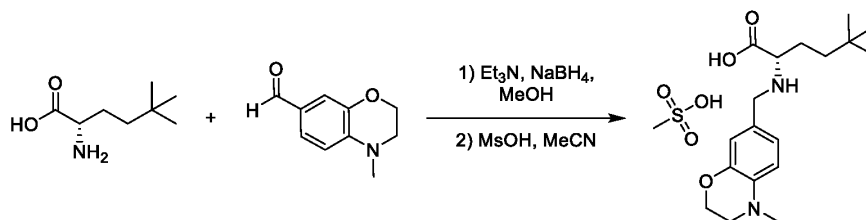
A sample of the freebase (61 mg, 0.15 mmol) was taken up in DCM (3 mL) and TFA (0.5 mL) was added. The mixture was stirred at rt for 1 hour before being diluted with MeOH (4 mL) and loaded on to SCX (~1 g). This was washed with MeOH and the required material was eluted with 7 M NH₃ in MeOH (5 column volumes) and concentrated. This was then solubilised in MeOH (2 mL) and 0.1 M MsOH in MeCN (1 equiv) was added before the material was concentrated to dryness to afford (S)-5,5-dimethyl-2-(((1,2,3,4-tetrahydroisoquinolin-6-yl)methyl)amino)hexanoic acid, Mesylic acid (67 mg, 0.16 mmol, 43 %, 98% Purity) as a colourless solid.

LCMS (Method #acid3minb, 0.13 min; M+H = 305.2. ¹H NMR (500 MHz, DMSO) δ 9.01 (s, 2H), 7.32 – 7.18 (m, 2H), 4.27 (s, 2H), 3.95 – 3.89 (m, 1H), 3.87 – 3.81 (m, 1H), 3.73 – 3.65 (m, 1H), 3.42 – 3.36 (m, 2H), 3.02 – 2.96 (m, 2H), 2.80 – 2.72 (m, 1H), 2.30 (s, 3H), 1.70 – 1.59 (m, 2H), 1.29 – 1.12 (m, 2H), 0.85 (s, 9H), 1 x exchangeable Hs not observed.

The following Examples were prepared in an analogous manner to Example 15, starting from the corresponding aldehyde.

Example	Structure	Yield	UPLC	NMR
16		70 mg, (43% yield, 95% purity)	Method #acid3minb, 1.09 min, M-H = 303.2	¹ H NMR (500 MHz, DMSO) δ 13.91 (s, 1H), 9.08 – 8.78 (m, 2H), 6.94 – 6.89 (m, 2H), 6.43 (d, J = 8.6 Hz, 1H), 5.92 (s, 1H), 3.99 – 3.87 (m, 2H), 3.87 – 3.72 (m, 1H), 3.18 (t, J = 5.6 Hz, 2H), 2.65 (t, J = 6.4 Hz, 2H), 2.29 (s, 3H), 1.91 – 1.62 (m, 4H), 1.30 (app. td, J = 13.2, 4.7 Hz, 1H), 1.10 (app. td, J = 12.9, 4.3 Hz, 1H), 0.85 (s, 9H).
17		93 mg, (65% yield, 98% purity)	Method #acid3minb, 1.14 min, M+H = 305.2	¹ H NMR (500 MHz, DMSO) δ 9.02 (v. br. s, 2H), 6.86 (d, J = 7.5 Hz, 1H), 6.49 – 6.43 (m, 2H), 5.82 (br. s, 1H), 3.96 – 3.85 (m, 2H), 3.76 – 3.73 (m, 1H), 3.17 (t, J = 5.5 Hz, 2H), 2.65 (t, J = 6.2 Hz, 2H), 2.29 (s, 3H), 1.86 – 1.69 (m, 4H), 1.31 (app. td, J = 13.1, 4.7 Hz, 1H), 1.11 (app. td, J = 12.9, 4.5 Hz, 1H), 0.85 (s, 9H), 1 x exchangeable not observed.

18		7.5 mg, (34% yield, 90% purity)	Method #acid3minb, 0.29 min, M+H = 305.2	¹ H NMR (500 MHz, DMSO) δ 9.01 (s, 2H), 7.29 (d, J = 7.9 Hz, 1H), 7.25 – 7.20 (m, 2H), 4.27 (s, 2H), 3.90 (d, J = 13.3 Hz, 1H), 3.80 (d, J = 13.1 Hz, 1H), 3.38 (t, J = 6.3 Hz, 2H), 3.19 – 3.14 (m, 1H), 2.98 (t, J = 6.3 Hz, 2H), 2.30 (s, 4H), 1.65 – 1.60 (m, 2H), 1.30 – 1.16 (m, 2H), 0.84 (s, 9H), 2 x exchangeable Hs not observed.
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Example 19

5 **Synthesis of (S)-5,5-dimethyl-2-(((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)methyl)amino)hexanoic acid, Mesylate**

A suspension of (S)-2-amino-5,5-dimethylhexanoic acid (112 mg, 1 Eq, 705 μmol), 4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carbaldehyde (125 mg, 1 Eq, 705 μmol) and Et₃N (71.9 mg, 99.0 μL, 1.01 Eq, 710 μmol) in MeOH (5.00 mL) was heated at 40 °C for 2.5 hours before being cooled with an ice bath and treated with NaBH₄ (27.0 mg, 1.01 Eq, 714 μmol). The mixture was then allowed to warm to rt and stir for 2.5 h before the reaction mixture was filtered. The solvent was removed *in vacuo* from the filtrate. The solid was

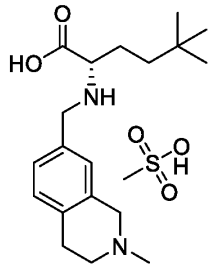
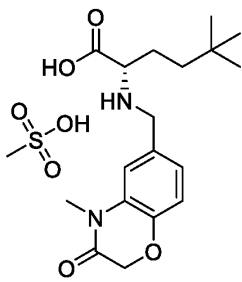
trituated with water (3 mL) before being filtered and washed with MeCN (5 mL) to afford a white solid. This material was purified by chromatography on RP Flash C18 (4 g cartridge, 5-40% (0.1 % Formic acid in MeCN) / (0.1% Formic Acid in Water)) to afford (S)-5,5-dimethyl-2-(((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)methyl)amino)hexanoic acid (29.0 mg, 86 μ mol, 12 %, 95% Purity) as a cream solid.

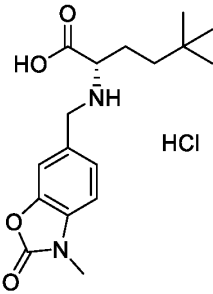
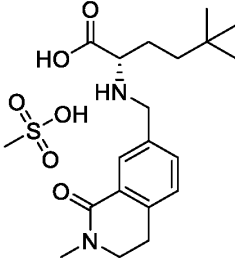
LCMS (Method #acid3minb, 1.34 min; M+H = 320.2. ¹H NMR (500 MHz, MeOD) δ 0.92 (s, 9H), 1.28 – 1.43 (m, 2H), 1.73 – 1.88 (m, 2H), 2.92 (s, 3H), 3.28 – 3.31 (m, 3H), 3.44 (t, J = 6.0 Hz, 1H), 3.95 (d, J = 13.0 Hz, 1H), 4.08 (d, J = 12.9 Hz, 1H), 4.26 – 4.31 (m, 2H), 6.74 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 2.1 Hz, 1H), 6.91 (dd, J = 2.1, 8.2 Hz, 1H).

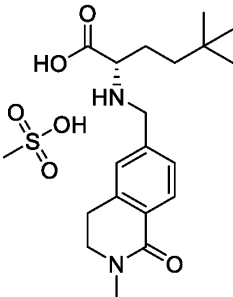
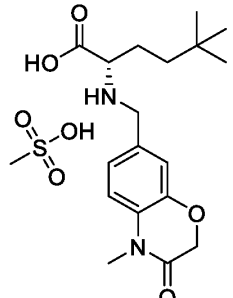
(S)-5,5-dimethyl-2-(((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)methyl)amino)hexanoic acid (29.0 mg, 95% Wt, 1 Eq, 86.0 μ mol) was stirred in MeOH (2.50 mL) before the addition of methanesulfonic acid (0.1 M in MeCN) (8.26 mg, 86.0 μ L, 0.10 molar, 1 Eq, 86.0 μ mol). The resultant solution was stirred at 25 °C for 30 min before being concentrated *in vacuo* to afford the product which was dried in the vacuum desiccator at 25 °C for 15 h. (S)-5,5-dimethyl-2-(((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)methyl)amino)hexanoic acid, Mesylate (27.0 mg, 64 μ mol, 75 %, 99% Purity) was afforded as a green/yellow solid.

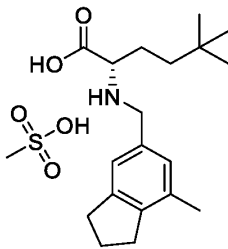
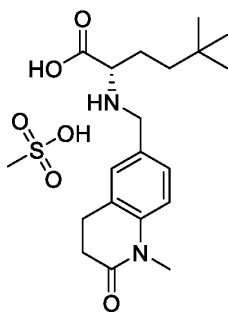
LCMS (Method #acid3minb, 0.97 min; M+H = 320.5. ¹H NMR (500 MHz, DMSO) δ 14.00 (bs, 1H), 9.07 (bs, 1H), 8.99 (bs, 1H), 6.85 (dd, J = 8.2, 2.1 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 4.25 – 4.20 (m, 2H), 4.00 – 3.97 (m, 2H), 3.81 (bs, 1H), 3.28 – 3.22 (m, 2H), 2.84 (s, 3H), 2.29 (s, 3H), 1.89 – 1.79 (m, 1H), 1.78 – 1.69 (m, 1H), 1.30 (td, J = 13.1, 4.7 Hz, 1H), 1.09 (td, J = 13.0, 4.3 Hz, 1H), 0.85 (s, 9H).

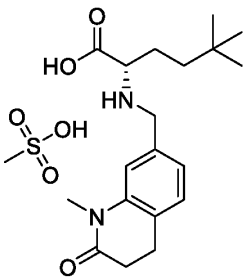
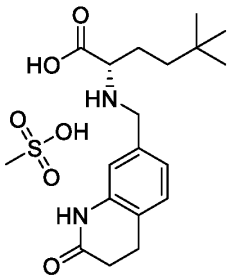
The following Examples can be prepared in an analogous manner to Example 19, starting from the corresponding aldehyde.

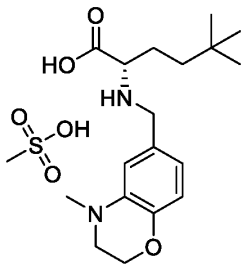
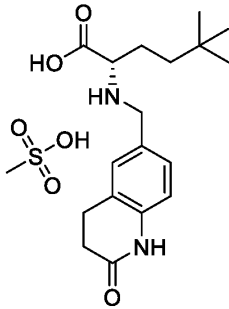
Ex.	Structure	Yield	UPLC	NMR
20		3.00 mg, (2.2% yield, 95% Purity)	Method #basic3mi nb, 1.12 min, M+H = 319.0	¹ H NMR (500 MHz, DMSO) δ 7.36 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.24 (s, 1H), 4.40 – 4.28 (m, 2H), 4.06 – 4.02 (m, 2H), 3.74 – 3.54 (m, 1H), 3.12 – 3.03 (m, 2H), 2.93 (s, 3H), 2.30 (s, 3H), 1.83 – 1.67 (m, 2H), 1.29 (app. td, J = 13.1, 4.9 Hz, 1H), 1.21 – 1.09 (m, 1H), 0.86 (s, 9H), CH ₂ obscured by residual solvent - not observed by HSQC, 3 x exchangeable Hs not observed.
21		30.0 mg, (19% yield, 98% Purity)	Method #acid3min b, 1.23 min, M+H = 335.2	¹ H NMR (500 MHz, DMSO) δ 13.99 (s, 1H), 9.47 (s, 2H), 7.43 (s, 1H), 7.12 (dd, J = 8.1, 1.9 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 4.68 (s, 2H), 4.14 (s, 2H), 3.89 – 3.79 (m, 1H), 1.96 – 1.71 (m, 2H), 1.32 (app. td, J = 13.1, 4.7 Hz, 1H), 1.17 – 1.07 (m, 1H), 0.86 (s, 9H).

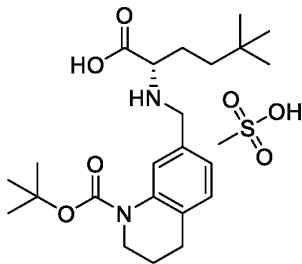
22		44 mg, (32% yield, 97% purity)	Method #basic3mi n, 0.62 min, M+H = 321.3	¹ H NMR (500 MHz, DMSO) δ 14.08 (br.s, 1H), 9.35 (br.s, 2H), 7.53 – 7.48 (m, 1H), 7.38 – 7.28 (m, 2H), 4.19 (s, 2H), 3.89 – 3.81 (m, 1H), 3.36 (s, 3H), 1.93 – 1.83 (m, 1H), 1.84 – 1.73 (m, 1H), 1.32 (app.td, J = 13.2, 4.7 Hz, 1H), 1.11 (app.td, J = 13.0, 4.3 Hz, 1H), 0.86 (s, 9H).
23		23.0 mg, (19% yield, 95% Purity)	Method #acid3min b, 1.28 min, M+H = 333.2	¹ H NMR (500 MHz, DMSO) δ 8.01 (s, 1H), 7.54 – 7.48 (m, 1H), 7.34 (d, J = 7.8 Hz, 1H), 4.12 – 4.08 (m, 2H), 3.74 – 3.62 (m, 1H), 3.55 (t, J = 6.7 Hz, 2H), 3.04 (s, 3H), 2.99 (t, J = 6.7 Hz, 2H), 2.29 (s, 3H), 1.81 – 1.66 (m, 2H), 1.29 (app. td, J = 12.8, 5.1 Hz, 1H), 1.18 – 1.07 (m, 1H), 0.85 (s, 9H), 3 x exchangeable Hs not observed.

24		70.0 mg, (59% yield, 95% Purity)	Method #acid3min b, 1.27 min, M+H = 333.2	¹ H NMR (500 MHz, DMSO) δ 9.25 (v. br. s, 2H), 7.91 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.39 (s, 1H), 4.16 (s, 2H), 3.93 – 3.89 (m, 1H), 3.56 (t, J = 6.7 Hz, 2H), 3.03 (s, 3H), 3.00 (t, J = 6.6 Hz, 2H), 2.29 (s, 3H), 1.87 – 1.73 (m, 2H), 1.32 (app. td, J = 13.1, 4.7 Hz, 1H), 1.18 – 1.09 (m, 1H), 0.86 (s, 9H), 1 x exchangeable H not observed
25		68.0 mg, (48% yield, 95% Purity)	Method #acid3min b, 1.25 min, M+H = 335.2	¹ H NMR (500 MHz, DMSO) δ 7.24 – 7.18 (m, 1H), 7.17 – 7.13 (m, 2H), 7.11 (s, 1H), 7.01 (s, 1H), 4.68 (s, 2H), 4.12 – 4.03 (m, 2H), 3.79 – 3.75 (m, 1H), 3.28 (s, 3H), 2.31 (s, 3H), 1.88 – 1.69 (m, 2H), 1.31 (app. td, J = 13.1, 4.7 Hz, 1H), 1.12 (app. td, J = 12.9, 4.4 Hz, 1H), 0.86 (s, 9H), 1 x exchangeable H not observed

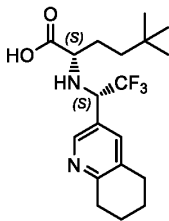
26		37.0 mg, (40% yield, 90% Purity)	Method #acid3min b, 1.60 min, M+H = 304.2	¹ H NMR (500 MHz, DMSO) δ 14.00 (s, 1H), 9.18 (s, 1H), 9.09 (s, 1H), 7.15 (s, 1H), 7.05 (s, 1H), 4.10 – 4.05 (m, 2H), 3.93 – 3.81 (m, 1H), 2.88 (t, J = 7.5 Hz, 2H), 2.80 (t, J = 7.4 Hz, 2H), 2.34 (s, 3H), 2.23 (s, 3H), 2.03 (app. p, J = 7.5 Hz, 2H), 1.91 – 1.72 (m, 2H), 1.32 (app. td, J = 13.1, 4.7 Hz, 1H), 1.15 – 1.05 (m, 1H), 0.85 (s, 9H).
27		15 mg, (11% yield, 95% Purity)	Method #acid3min b, 1.25 min, M-H = 331.2	¹ H NMR (500 MHz, DMSO) δ 7.35 (dd, J = 8.3, 2.1 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 4.11 – 4.02 (m, 2H), 3.79 – 3.76 (m, 1H), 3.26 (s, 3H), 2.91 – 2.85 (m, 2H), 2.58 – 2.52 (m, 2H), 2.29 (s, 3H), 1.85 – 1.69 (m, 2H), 1.31 (app. td, J = 13.1, 4.8 Hz, 1H), 1.13 (app. td, J = 13.0, 4.6 Hz, 1H), 0.86 (s, 9H), 3 x exchangeable Hs not observed.

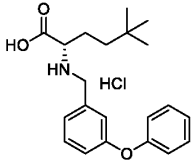
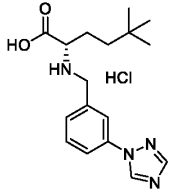
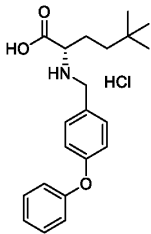
28		98 mg, (59% yield, 98% Purity)	Method #acid3min b, 1.29 min, M+H = 333.2	¹ H NMR (500 MHz, DMSO) δ 9.16 (s, 2H), 7.28 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 1.6 Hz, 1H), 7.09 (dd, J = 7.5, 1.6 Hz, 1H), 4.20 – 4.10 (m, 2H), 3.86 – 3.82 (m, 1H), 3.27 (s, 3H), 2.91 – 2.85 (m, 2H), 2.57 – 2.51 (m, 2H), 2.29 (s, 3H), 1.89 – 1.70 (m, 2H), 1.31 (app. td, J = 13.1, 4.6 Hz, 1H), 1.16 – 1.10 (m, 1H), 0.86 (s, 9H) 1 x OH not observed.
29		23 mg, (26% yield, 95% Purity)	Method #acid3min b, 1.23 min, M+H = 319.2	¹ H NMR (500 MHz, DMSO) δ 10.30 (s, 1H), 9.30 – 9.04 (m, 2H), 7.24 (d, J = 7.7 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.92 (d, J = 1.7 Hz, 1H), 4.09 – 4.05 (m, 2H), 3.95 – 3.92 (m, 1H), 2.89 (t, J = 7.6 Hz, 2H), 2.47 – 2.43 (m, 2H), 2.30 (s, 3H), 1.88 – 1.73 (m, 2H), 1.32 (app. td, J = 13.2, 4.7 Hz, 1H), 1.11 (app. td, J = 12.8, 4.2 Hz, 1H), 0.86 (s, 9H), 1 x OH not observed

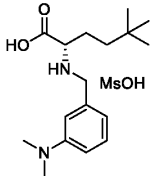
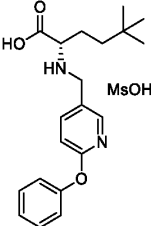
30		70 mg, (45% yield, 90% Purity)	Method #acid3min b, 1.49 min, M-H = 319.2	¹ H NMR (500 MHz, DMSO) δ 6.80 (d, J = 1.9 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.65 – 6.60 (m, 1H), 4.24 – 4.21 (m, 2H), 4.02 – 3.89 (m, 2H), 3.61 – 3.58 (m, 1H), 3.24 (t, J = 4.4 Hz, 2H), 2.84 (s, 3H), 2.29 (s, 3H), 1.79 – 1.68 (m, 2H), 1.29 (app. td, J = 13.1, 4.7 Hz, 1H), 1.13 (app. dt, J = 13.0, 6.8 Hz, 1H), 0.84 (s, 9H), 3 x exchangeable Hs not observed.
31		17 mg, (11% yield, 95% Purity)	Method #acid3min b, 1.28 min, M+H = 319.2	¹ H NMR (500 MHz, DMSO) δ 10.20 (s, 1H), 7.26 (s, 1H), 7.24 – 7.19 (m, 1H), 6.87 (d, J = 8.1 Hz, 1H), 4.06 – 3.94 (m, 2H), 3.77 – 3.73 (m, 1H), 2.89 (t, J = 7.5 Hz, 2H), 2.48 – 2.44 (m, 2H), 2.29 (s, 3H), 1.86 – 1.66 (m, 2H), 1.29 (app. dt, J = 13.2, 6.7 Hz, 1H), 1.16 – 1.08 (m, 1H), 0.85 (s, 9H), 3 x exchangeable Hs not observed

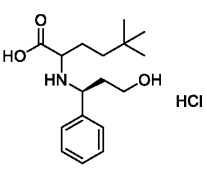
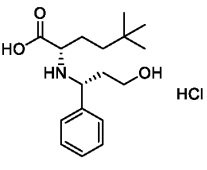
32		13 mg, (80% yield, 98% Purity)	Method #acid3min , 1.72 min, M+H = 405.2	¹ H NMR (500 MHz, DMSO) δ 9.10 (br. s, 2H), 7.76 (s, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.11 – 7.05 (m, 1H), 4.13 – 4.00 (m, 2H), 3.85 – 3.74 (m, 1H), 3.66 – 3.56 (m, 2H), 2.73 (t, J = 6.5 Hz, 2H), 2.29 (s, 3H), 1.88 – 1.68 (m, 4H), 1.48 (s, 9H), 1.37 – 1.27 (m, 1H), 1.13 (app. td, J = 12.9, 4.4 Hz, 1H), 0.85 (s, 9H), 1 x exchangeable H not observed.
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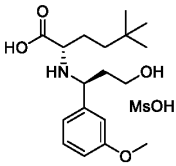
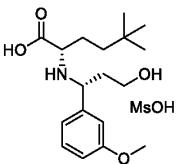
The following Examples were prepared in an analogous manner to the other examples, starting from their corresponding ketone, aldehyde, or ester.

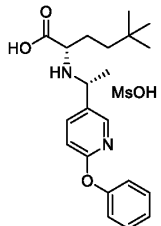
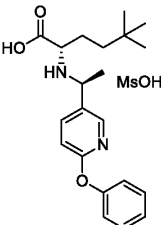
Example	Structure	Yield	LCMS	NMR
33		19.5 mg (16% yield, 98. 21% purity)	Method 7, 1.123 min; M+H = 373.2; calcd. 373.2	¹ H-NMR (400 MHz, DMSO) δ 8.31 (d, J = 2.3 Hz, 1H), 7.53 (s, 1H), 4.36 (q, J = 8.2 Hz, 1H), 3.14 (s, 2H), 2.84 – 2.70 (m, 5H), 1.85 – 1.73 (m, 4H), 1.66 – 1.37 (m, 2H), 1.23 (dt, J = 11.8, 5.8 Hz, 2H), 0.85 (s, 9H).

34		1.4 mg (2% yield, 97.62% purity)	Method 1, 1.179 min; M+H-HCl = 342.6; calcd. 342.2	
35		7.2 mg (16% yield, 98.96% purity)	Method 1, 1.083 min; M+H-HCl- = 317.2; calcd. 317.2	
36		1.0 mg (2% yield, 98.49% purity)	Method 1, 1.262 min; M+H-HCl- = 342.3; calcd. 342.2	

37		40.5 mg (31% yield, 97.54% purity)	Method 1, 0.990 min; M+H- MsOH = 293.2; calcd. 293.2	¹ H-NMR (400 MHz, DMSO) δ 9.32 – 9.09 (m, 2H), 7.28 – 7.20 (m, 1H), 6.86 (s, 1H), 6.79 (d, <i>J</i> = 8.0 Hz, 1H), 6.75 (d, <i>J</i> = 7.5 Hz, 1H), 4.14 – 4.06 (m, 2H), 3.90 – 3.85 (m, 1H), 2.31 (s, 3H), 1.88 – 1.71 (m, 2H), 1.32 (td, <i>J</i> = 13.1, 4.8 Hz, 1H), 1.12 (td, <i>J</i> = 12.9, 4.4 Hz, 1H), 0.86 (s, 9H).
38		50.4 mg (9% yield, 100% purity)	Method 1, 0.999 min; M+H- MsOH- = 343.5; calcd. 343.2	¹ H-NMR (400 MHz, DMSO) δ 8.18 (d, <i>J</i> = 2.5 Hz, 1H), 7.92 (dd, <i>J</i> = 8.4, 2.4 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.29 – 7.21 (m, 1H), 7.14 – 7.11 (m, 1H), 7.11 – 7.07 (m, 2H), 4.14 – 3.97 (m, 2H), 3.80 – 3.71 (m, 1H), 2.29 (s, 3H), 1.82 – 1.69 (m, 2H), 1.28 (td, <i>J</i> = 12.8, 5.4 Hz, 1H), 1.14 (td, <i>J</i> = 12.6, 5.0 Hz, 1H), 0.86 (s, 9H).

39 ^{1,2}		20.8 mg (39% yield, 98.81% purity)	Method 7, 0.896 min; M+H-HCl- = 294.2; calcd. 294.2	¹ H-NMR (400 MHz, DMSO) δ 10.21 – 9.33 (m, 2H), 7.62 – 7.35 (m, 5H), 4.38 (brs, 1H), 3.59 (brs, 1H), 3.39 – 3.17 (m, 2H), 3.09 – 2.99 (m, 1H), 2.36 (brs, 1H), 2.10 (brs, 1H), 1.98 – 1.65 (m, 2H), 1.34 – 1.16 (m, 1H), 1.09 – 0.94 (m, 1H), 0.90 – 0.75 (m, 9H).
40 ¹		60.7 mg (56% yield, 98.95% purity)	Method 1, 0.871 min; M+H-HCl- = 294.5; calcd. 294.2	¹ H-NMR (400 MHz, DMSO) δ 9.44 (br, 2H), 7.63 – 7.35 (m, 5H), 4.79 (brs, 1H), 4.40 – 4.32 (m, 1H), 3.63 – 3.55 (m, 1H), 3.31 – 3.27 (m, 1H), 3.10 – 3.04 (m, 1H), 2.38 – 2.29 (m, 1H), 2.11 – 2.05 (m, 1H), 1.92 – 1.85 (m, 1H), 1.78 – 1.68 (m, 1H), 1.27 (td, <i>J</i> = 13.2, 4.8 Hz, 1H), 1.01 (td, <i>J</i> = 13.1, 4.2 Hz, 1H), 0.85 (s, 9H).

41		23.4 mg (36% yield, 96.59% purity)	Method 1, 0.907 min; M+H- MsOH- = 324.4; calcd. 324.2	¹ H-NMR (400 MHz, DMSO) δ 9.30 (brs, 2H), 7.39 (t, <i>J</i> = 7.9 Hz, 1H), 7.05 (t, <i>J</i> = 2.1 Hz, 1H), 7.01 (dd, <i>J</i> = 8.1, 2.5 Hz, 1H), 6.98 (d, <i>J</i> = 7.6 Hz, 1H), 5.01 – 4.56 (brs, 1H), 4.39 – 4.30 (m, 1H), 3.77 (s, 3H), 3.41 – 3.38 (m, 1H), 3.09 (td, <i>J</i> = 10.3, 4.5 Hz, 1H), 2.37 – 2.25 (m, 4H), 2.06 – 1.94 (m, 1H), 1.78 – 1.57 (m, 2H), 1.20 (td, <i>J</i> = 12.9, 5.1 Hz, 1H), 1.06 (td, <i>J</i> = 12.7, 4.8 Hz, 1H), 0.80 (s, 9H). 1H missing
42		18.3 mg (28% yield, 99.05% purity)	Method 1, 0.898 min; M+H- MsOH- = 324.4; calcd. 324.2	¹ H NMR (400 MHz, DMSO) δ 9.28 (brs, 2H), 7.37 (t, <i>J</i> = 7.9 Hz, 1H), 7.10 (t, <i>J</i> = 2.1 Hz, 1H), 7.04 (d, <i>J</i> = 7.5 Hz, 1H), 7.00 (dd, <i>J</i> = 8.3, 2.5 Hz, 1H), 4.98 - 4.62 (brs, 1H), 4.43 – 4.30 (m, 1H), 3.78 (s, 3H), 3.61 – 3.54 (m, 1H), 3.16 – 3.06 (m, 1H), 2.31 – 2.22 (m, 4H), 2.10 – 1.98 (m, 1H), 1.92 – 1.81 (m, 1H), 1.77 – 1.63 (m, 1H), 1.32 – 1.20 (m, 1H), 1.01 (td, <i>J</i> = 12.8, 4.0 Hz, 1H), 0.86 (s, 9H). 1H missing

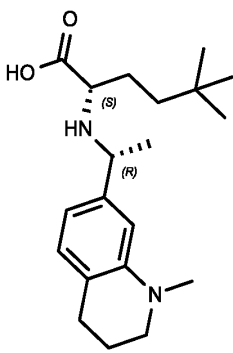
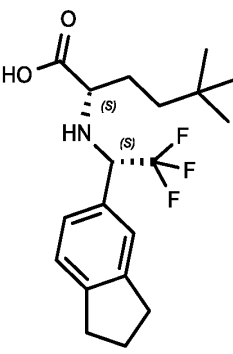
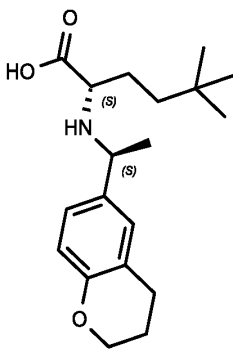
43		28.8 mg (14% yield, 100% purity)	Method 7, 1.046 min; M+H- MsOH = 357.2; calcd. 357.2	¹ H-NMR (400 MHz, DMSO) δ 9.42-8.72 (br, 2H), 8.21 (d, <i>J</i> = 2.5 Hz, 1H), 7.97 (dd, <i>J</i> = 8.6, 2.5 Hz, 1H), 7.44 (t, <i>J</i> = 7.9 Hz, 2H), 7.24 (t, <i>J</i> = 7.4 Hz, 1H), 7.12 (dd, <i>J</i> = 8.4, 6.7 Hz, 3H), 4.47 – 4.34 (m, 1H), 3.81 – 3.68 (m, 1H), 2.29 (s, 3H), 1.87 – 1.75 (m, 1H), 1.75 – 1.64 (m, 1H), 1.57 (d, <i>J</i> = 6.7 Hz, 3H), 1.26 (td, <i>J</i> = 13.2, 4.8 Hz, 1H), 1.08 (dt, <i>J</i> = 12.4, 4.0 Hz, 1H), 0.86 (s, 9H).
44		30.4 mg (13% yield, 100% purity)	Method 7, 1.049 min; M+Na- MsOH = 357.2; calcd. 357.2	¹ H-NMR (400 MHz, DMSO) δ 8.12 (s, 1H), 7.93 (d, <i>J</i> = 8.6 Hz, 1H), 7.43 (t, <i>J</i> = 7.9 Hz, 2H), 7.23 (t, <i>J</i> = 7.4 Hz, 1H), 7.13 (d, <i>J</i> = 7.6 Hz, 3H), 7.09 (d, <i>J</i> = 8.5 Hz, 1H), 4.22 (s, 1H), 2.30 (s, 3H), 1.67 – 1.56 (m, 2H), 1.50 (d, <i>J</i> = 7.4 Hz, 3H), 1.15 (t, <i>J</i> = 7.9 Hz, 2H), 0.82 (s, 9H).

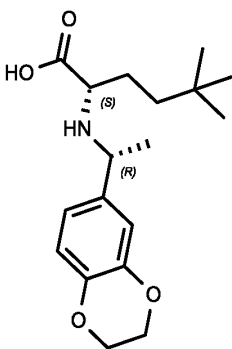
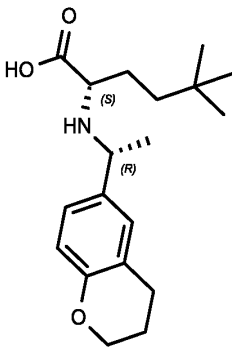
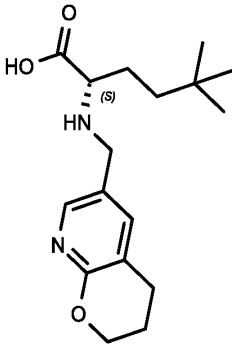
¹ was reformatted using HCl instead of 1 equiv MsOH

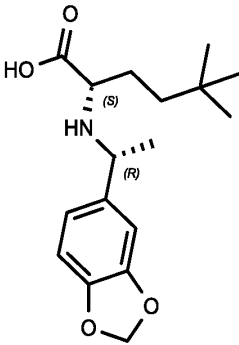
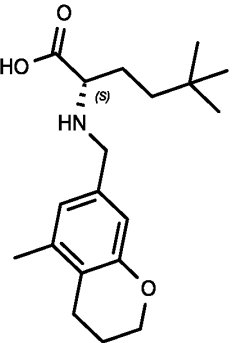
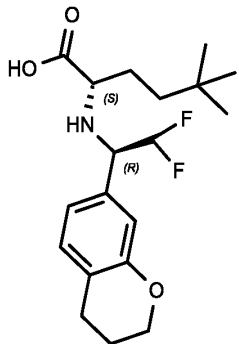
² reaction performed using racemic triflate

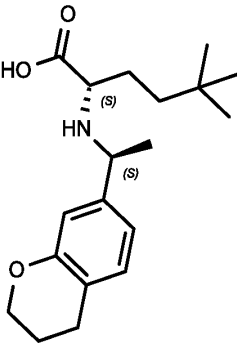
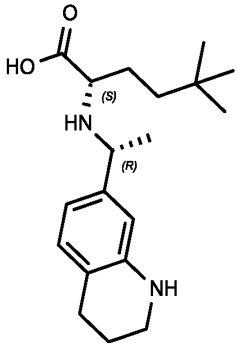
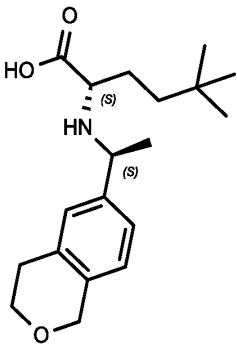
The following examples were synthesised in an analogous manner to the other
5 examples.

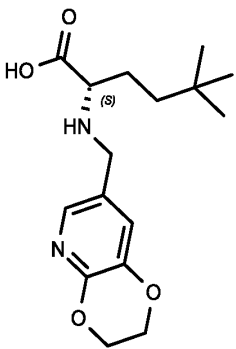
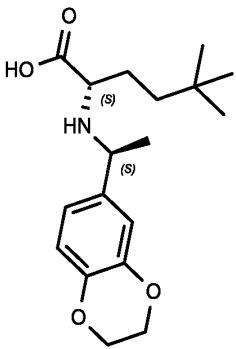
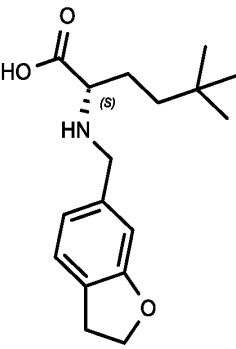
Example	Structure
45	 <chem>CC(C)(C)CC[C@H](C(=O)O)N[C@@H](C1=CC=C2CCCCC2=C1)C(F)F</chem>
46	 <chem>CC(C)(C)CC[C@H](C(=O)O)N[C@@H](C1=CC=C2CCOC2=C1)C(F)F</chem>
47	 <chem>CC(C)(C)CC[C@H](C(=O)O)N[C@@H](C1=CC=C2CCCCC2=C1)C(F)(F)F</chem>

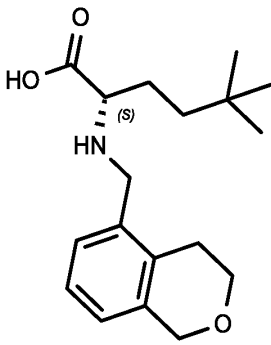
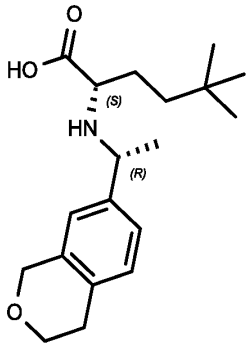
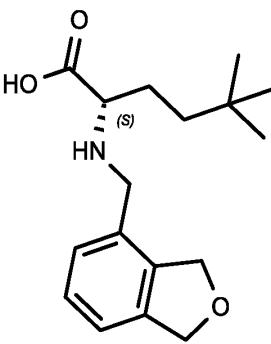
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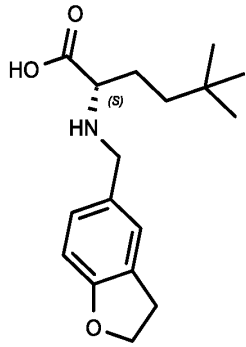
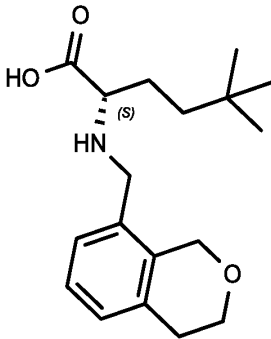
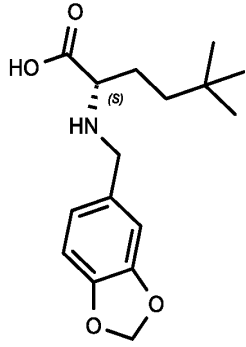
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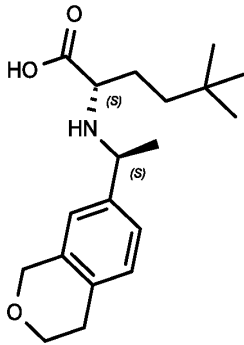
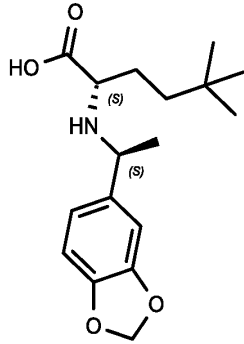
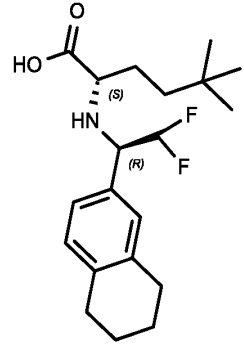
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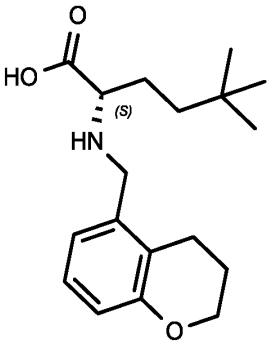
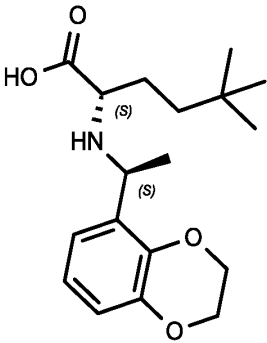
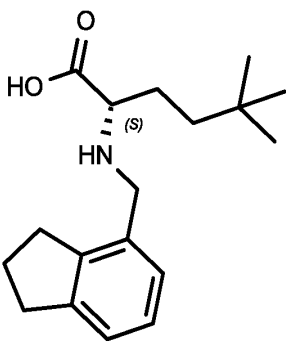
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60	 Chemical structure of compound 60: A carboxylic acid derivative with a (S)-chiral center, a tert-butyl group, and a 2,3-dihydro-4H-benzofuro[2,3-b]pyridine moiety.
61	 Chemical structure of compound 61: A carboxylic acid derivative with a (S)-chiral center, a tert-butyl group, and a 2,3-dihydro-4H-benzofuro[2,3-b]pyridine moiety.
62	 Chemical structure of compound 62: A carboxylic acid derivative with a (S)-chiral center, a tert-butyl group, and a 2,3-dihydro-4H-benzofuro[2,3-b]pyridine moiety.

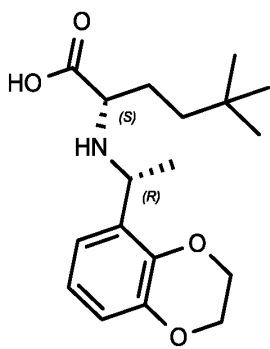
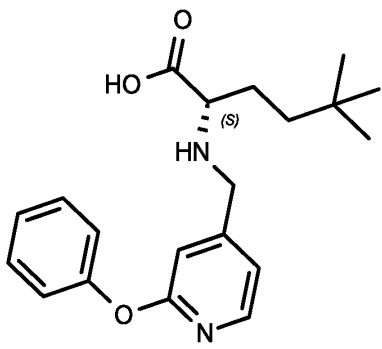
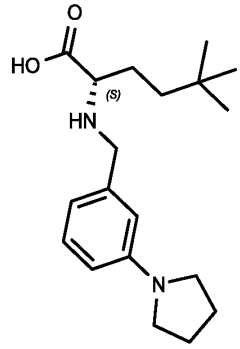
63	 <chem>CC(C)(C)CC[C@H](NCc1ccc2c(c1)OCC2)C(=O)O</chem>
64	 <chem>CC(C)(C)CC[C@H](NCc1ccc2c(c1)OCC2)C(=O)O</chem>
65	 <chem>CC(C)(C)CC[C@H](NCc1ccc2c(c1)OCC2)C(=O)O</chem>

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BIOLOGICAL DATA

Neurotensin scintillation proximity assay

The exemplified compounds of the invention were tested in a Neurotensin (NTS) scintillation proximity assay (SPA). The IC₅₀ data is shown in the table below. NTS, which is a 13 amino acid neuropeptide, is a sortilin ligand. The IC₅₀ is a measure of the amount of the compound required to inhibit the binding of NTS to sortilin by 50%. The skilled person will recognise that the lower the IC₅₀ value, the less of the compound needed to achieve the desired effect, and as a result, the chances of undesirable off-target effects are reduced.

Compound affinity was determined by measuring the displacement of [³H]-neurotensin binding to *h*-Sortilin in SPA format. Total volume of 40 µl in 50 mM HEPES pH 7.4 assay buffer containing 100 mM NaCl, 2.0 mM CaCl₂, 0.1% BSA and 0.1% Tween-20. Compound pre-incubation for 30 minutes at room temperature with 150 nM of 6his-Sortilin before 5 nM [³H]-Neurotensin and Ni chelate imaging beads (Perkin Elmer) were added, after 6 hours the plate was read on a ViewLux with 360 s exposure time. Dose-response evaluation of compounds was performed with 8 concentrations of drugs (covering 3 decades). IC₅₀ values were calculated by nonlinear regression using the sigmoid concentration-response (variable slope) using CDD Vault software. All values reported are average of at least 2 determinations.

The data in the table below shows that the compounds of the invention are sortilin inhibitors.

Example	IC ₅₀ [³ H]Neurotensin SPA (µM)
1	0.27
2	0.35
3	0.23
4	0.12
5	0.31
6	0.21
7	0.14

8	0.5
9	0.21
10	0.64
11	0.12
12	0.61
13	0.21
14	0.28
15	0.9
16	0.57
17	0.19
18	0.5
19	0.66
20	0.47
21	0.26
22	0.47
23	0.43
24	0.63
25	0.95
26	0.52
27	0.76
28	0.22
29	0.29
30	0.35
31	0.9
32	0.13
33	0.13
34	0.82
35	0.96
36	0.52
37	0.57
38	0.34
39	0.41
40	6.45
41	0.76
42	0.59
43	0.41
44	0.74
45	0.12
46	0.13
47	0.16
49	0.22
50	0.23

51	0.28
52	0.26
53	0.58
54	0.38
55	0.31
56	0.31
57	0.3
58	0.31
59	0.32
60	0.82
61	0.35
62	0.43
63	0.65
64	0.42
65	0.62
66	0.7
67	0.5
68	0.86
69	0.59
70	0.53
71	0.59
72	1.08
73	0.65
74	0.85
75	1.22
76	0.23
77	0.35

Creoptix (GCI) method – using SEQ ID NO. 4 (Murine sortillin)

- The GCI assay is based upon understood surface plasmon resonance methodologies specifically enhanced for detecting the binding of small entities to proteins. A protein, bound to a surface, is bathed in a solution containing potential ligands giving rise to binding kinetics to generate K_{on} and K_{off} rates, as well as a K_d . This methodology does not require the use of additional tracers and can be used with or without the element of competition with known ligands.

Reagents:

Reagent	Part no	Supplier
DMSO	D8418	Sigma
Borate	B BELU-50	Xantec Bioanalytics
EDTA	E7889-100ML	Merck Life Science UK
HBS-N	BR-1006-70	Cytiva
4PCH wave chip	4PCH	Creoptix AG
rhSortilin	3154-ST-050	Bio-Techne Ltd
rmSortilin	2934-ST-050	Bio-Techne Ltd
EDC	BR100050	Cytiva
NHS	BR100050	Cytiva
Acetate pH 5.0	BR100351	Cytiva
Trizma/ Tris	93352-1KG	Merck Life Science UK

All buffers described were filtered using a 0.2µm filter (Product number: 10300461, Nalgene) and degassed for 15 minutes prior to use.

- 5 A flow cell temperature of 25 degrees Celsius was used throughout the experiment.

Chip conditioning and immobilisation

A 4PCH chip was conditioned across all flow cells using 0.2 X concentration running buffer (running buffer composition: 1XHBS-N, pH 7.4, 3.4 mM EDTA, 1%

DMSO) using pre-set conditioning wizard (WAVE control software) injecting: 0.1 M borate, 1 M NaCl (pH 9) followed by three start-up injections of 0.2 X running buffer.

A buffer exchange was performed and 1x running buffer (1XHBS-N, pH 7.4, 3.4 mM EDTA, 1% DMSO) used during the immobilisation procedure:

An initial injection of EDC/NHS (mixed in 1:1 ratio) was performed across all 4-flow cells to activate the surface for amine coupling of ligands.

Recombinant Sortilin aliquots were thawed quickly by hand and centrifuged at 13,300 rpm for 10 minutes. A 10 µg/ml protein solution was then made in pH 5.0 acetate and injected once for 20 minutes over flow-cells 2, 3 and 4 for human, human (flow cells 2 & 3), and mouse Sortilin respectively followed by a 60 second dissociation period.

A final 7-minute passivation injection of 50 mM tris was used across all flow cells.

A flow rate of 10 µl/min was used for all conditioning and immobilisation cycles.

15 **Rapid Kinetics: Intermediate binders**

Compounds were screened at 1 µM using the in-built 'intermediate binders' settings: 100 ul/min, 45 s baseline, 25 s association, 300 s dissociation, with blanks every 5th sample and a DMSO correction (1.5 % DMSO at the start and end of the experiment as well as every 20 cycles. An acquisition rate of 10 Hz was used throughout the experiment.

Compounds were screened at a final assay concentration of 1 µM and a final DMSO concentration was 1 %. To achieve this, compounds were diluted in DMSO from 10 mM stocks to 100 µM (100 x final assay concentration) then diluted 1:100 in running buffer which contained no DMSO to establish a final assay concentration of compound of 1 µM and a final DMSO concentration of 1 % [DMSO].

Compounds and DMSO were mixed by plate shaking at 1000 rpm for 60 seconds using a Bioshake instrument.

A flow rate of 100 µl/min was used throughout the experiment.

Data Evaluation:

- 5 Data was evaluated using the RAPID kinetic analysis tool in the GCI WAVE_control software with data fitted using a standard 1:1 kinetic BioModel.

The results for compounds of the invention are shown in the table below.

Example	Form of Compound	Species	KD (M) Sortilin
1	Free base	Human	1.07E-07
2	Free base	Human	1.72E-07
3	Free base	Human	2.37E-07
3	Free base	Mouse	6.50E-08
3	Mesylate salt	Human	5.20E-08
4	Free base	Human	4.09E-08
4	HCl salt	Human	5.17E-08
4	Mesylate salt	Human	4.25E-08
5	Free base	Human	6.34E-08
6	Free base	Human	1.17E-07
7	Free base	Human	2.64E-07
8	Free base	Human	1.91E-07
9	Free base	Human	2.27E-07
9	Free base	Mouse	6.00E-08
9	Mesylate salt	Human	6.49E-08
9	Mesylate salt	Mouse	5.95E-08
10	Free base	Human	2.00E-07
10	Free base	Mouse	2.41E-07
11	Free base	Human	3.66E-08
11	Mesylate salt	Human	4.07E-08
13	Mesylate salt	Human	5.75E-08
14	Mesylate salt	Human	3.51E-08
16	Free base	Human	2.55E-07

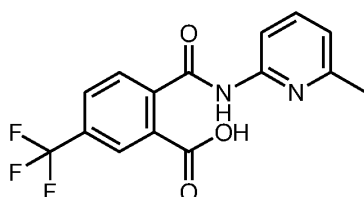
16	Free base	Mouse	2.99E-07
17	Free base	Human	9.73E-08
18	Free base	Human	1.42E-06
18	Free base	Mouse	2.28E-06
19	Free base	Human	3.72E-06
19	Free base	Mouse	3.18E-06
21	Free base	Human	1.64E-07
22	Free base	Human	3.50E-07
25	Free base	Human	5.63E-07
25	Free base	Human	1.58E-07
28	Free base	Human	3.17E-07
30	Free base	Human	5.07E-06
30	Free base	Mouse	7.60E-06
33	Free base	Human	2.80E-08
34	Free base	Human	2.16E-07
38	Mesylate salt	Human	4.91E-08
43	Free base	Human	6.83E-08
44	Free base	Human	1.27E-07
45	Free base	Human	4.39E-08
46	Free base	Human	4.34E-08
47	Free base	Human	7.53E-08
48	Free base	Human	4.62E-08
49	Free base	Human	5.04E-07
50	Free base	Human	1.20E-07
50	Free base	Mouse	2.58E-07
50	Mesylate salt	Human	2.21E-07
50	Mesylate salt	Mouse	2.58E-07
51	Free base	Human	1.81E-07
52	Free base	Human	3.84E-07
52	Mesylate salt	Human	1.33E-07
52	Mesylate salt	Mouse	1.29E-07
54	Free base	Human	1.05E-07
56	Free base	Human	6.96E-07
58	Free base	Human	6.70E-08
58	Free base	Mouse	7.03E-08
59	Mesylate salt	Human	2.18E-07
59	Mesylate salt	Mouse	2.04E-07
61	Free base	Human	1.44E-07
68	Free base	Human	1.63E-07
70	Free base	Human	1.33E-07

70	Free base	Mouse	1.16E-07
71	Free base	Human	1.93E-07
72	Free base	Human	6.13E-07
76	Free base	Human	5.83E-08

- For compounds of the invention it is advantageous to have K_d lower than $1.00 \text{ E-}4$. The K_d data generated demonstrate that examples of the invention bind directly to the sortilin protein and bind in a generally similar manner in both human and murine sortilin protein which is advantageous for the development of non-human models of pharmacokinetics and disease.

BLOOD-BRAIN-BARRIER PERMEABILITY

- To determine whether the compounds of the invention are capable of crossing the blood brain barrier, the K_{puu} was calculated for Example 3 and Comparative Example 1, which is a sortilin modulator that is not in accordance with the invention and has the following structure:



Plasma protein binding and brain homogenate binding for study compounds in mouse, dog, and rat by rapid equilibrium dialysis

- Mice were dosed with the compound of Comparative Example 1 and rats and dogs were dosed with the compound of Example 3, and then the plasma and brain were removed at specific timepoints to be analysed for compound concentration. Separately, the fraction of compound bound to plasma protein or brain homogenate was measured to allow assessment of free fractions.
- The free drug hypothesis states that only unbound compound is able to permeate through biological membranes, interact with and elicit a pharmacological effect.

Therefore, it is desirable for compounds to have a high free brain concentration. However, only the free unbound drug fraction is subject to Clearance mechanisms.

In practice, unbound fractions in plasma and brain tissue were assessed using rapid equilibrium dialysis *in vitro*. Separately a pharmacokinetic study was run *in vivo* whereby a dose of the compound of interest was given at T=0 hours and at subsequent timepoints (eg 0.5, 1 and 4 hours) plasma and separately brain samples were analysed for total concentration of the compound of interest. These total concentrations could then be adjusted with the unbound fraction to give the unbound concentrations in the plasma and brain. The unbound partition coefficient (K_{puu}) was then determined as a ratio between the free compound concentrations in the compartment of interest, here the brain/CNS and the plasma.

Rapid equilibrium dialysis

The test compounds were incubated in plasma and brain homogenate from the relevant species at 37 °C in RED device with inserts (8K MWCO, Thermo scientific) for 4 hours at 5 µM in triplicates. 350 µL of 150 mM phosphate buffered saline (PBS, pH 7.4) was used as the receiver side solutions. The samples were collected from both sides after 4 hours equilibration time and their matrices were made similar by diluting the donor side sample using blank PBS, and by diluting the receiver side sample using blank plasma/phosphate buffered saline. After the incubation, aliquots of donor side matrixes were diluted with an equal volume of the blank receiver side matrix and aliquots of receiver side matrixes were diluted with an equal volume of blank donor side matrix. All samples were protein precipitated by addition of a two-fold volume of acetonitrile containing 100 nM of repaglinide as an internal standard. After 10-minute centrifugation at 13 200 rpm, the sample supernatants were analysed with an LC-MS/MS, to obtain the unbound fraction of the test compound (F_{ub}). The unbound fraction was calculated from the peak area ratios obtained for each matrix:

$$F_{ub} = C_{PBS} / C_{plasma};$$

where C_{PBS} and C_{plasma} are the analyte concentrations in PBS (receiver) and plasma (donor), respectively.

Recovery samples were prepared in each condition but without dialysis, and were used for evaluation of recovery from the dialysis experiment using following

5 formula:

$$\% \text{ Recovery} = 100 \times (V_{\text{PBS}} \times C_{\text{PBS}} + V_{\text{plasma}} \times C_{\text{plasma}}) / V_{\text{plasma}} \times C_{\text{recovery}}$$

where V_{PBS} is the volume on the receiver side (PBS) and V_{plasma} is the volume on donor side (plasma) of the dialysis device. C_{recovery} is the analyte concentration
10 measured from the recovery sample.

Propranolol (1 μ M) and fluoxetine (5 μ M) were included in the experiment as a control compounds.

The unbound fraction in brain ($F_{\text{ub, brain}}$) was calculated from the measured value in brain homogenate ($F_{\text{ub, meas}}$), taking into account the dilution factor used in
15 preparing the brain homogenate:

$$F_{\text{ub, brain}} = \frac{1/D}{\left(\frac{1}{F_{\text{ub, meas}}}\right) - 1 + \left(\frac{1}{D}\right)}$$

where D = dilution factor (here 5).

Analytical method

Instrumentation: Waters Acquity UPLC + Waters Xevo TQ-XS triple quadrupole
20 MS

Column: Waters Acquity HSS T3 (2.1x50mm, 1.8 μ m) column with pre-column filter

Gradient Elution; A = 0.1% Formic acid, B = Acetonitrile

Time (min)	Flow	A%	B%	Curve
0.000	0.500 ml/min	95	5	-
0.500	0.500 ml/min	95	5	6
2.500	0.500 ml/min	25	75	6
3.500	0.500 ml/min	2	98	1
4.500	0.500 ml/min	95	5	1

Temperature: 40 °C

Injection Volume: 1.5 µl

Ion Source: ESI+

5 Capillary voltage: 2400 V

Source temperature: 150 °C

Desolvation temperature: 650 °C

Cone gas flow: 240 L/hr

Desolvation gas flow: 1200 L/hr

10 Nebuliser gas flow: 7 Bar

Collision gas flow: 0.15 mL/min

Software: MassLynx 4.2

Compound	MRM transition	Collision energy (V)	Cone (V)	Retention time
Example 3	306 > 117			
	325 > 92	32	46	2.11

Comparative Example 1	325 > 109*	16	46	
	325 > 217	26	64	
Propranolol	260 > 116*	18	50	1.78
	260 > 155	23	50	
	260 > 183	25	50	
Fluoxetine	310 > 148*	6	30	2.03

* MRM trace used for quantification

Results of Equilibrium Dialysis

- 5 The table below shows, for the mouse plasma, mouse brain, rat brain and dog plasma, the unbound fractions of compounds Example 3 and the Comparative Example 1 in plasma and brain homogenate.

	Mouse Plasma	Mouse Brain	Rat Brain	Dog plasma
	Unbound (Fu, %)	Unbound (Fu, %)	Unbound (Fu, %)	Unbound (Fu, %)
Example 3			37.1	55.5
Comparative Example 1	6.8	27.3		

10 Blood-brain-barrier permeability of study compounds in mice after IV administration

The compound is administered to the animal in a suitable vehicle at T=0 hours. At 0.5 hours post administration plasma and separately brain are removed, prepared and analysed for total compound concentration.

General sample processing procedure (Plasma):

Protein precipitation (PPT) using 96-well plate

- 1). An aliquot of 5 μL unknown sample, calibration standard, quality control and dilution quality control (if have), single blank, and double blank sample was added to the 96-well plate respectively;
- 2). Each sample (except the double blank) was quenched with 200 μL of IS1 (6 in 1 internal standard in MeOH (Labetalol & tolbutamide & Verapamil & dexamethasone & glyburide & Celecoxib 100 ng/mL for each) respectively (double blank sample was quenched with 200 μL of MeOH), and then the mixture was vortex-mixed for 10 min at 800 rpm and centrifuged for 15 min at $3220 \times g$, 4°C ;
- 3). An aliquot of 60 μL supernatant was transferred to another clean 96-well plate and centrifuged for 5 min at $3220 \times g$, 4°C , then the supernatant was directly injected for LC-MS/MS analysis.

Dilution procedure description:

- 1) Dilution factor as 10 : An aliquot of 2 μL unknown sample was added with 18 μL blank matrix;

General sample processing procedure (Brain homogenate):

Protein precipitation (PPT) using 96-well plate

- 1). An aliquot of 20 μL unknown sample, calibration standard, quality control and dilution quality control (if have), single blank, and double blank sample was added to the 96-well plate respectively;
- 2). Each sample (except the double blank) was quenched with 800 μL of IS1 respectively (double blank sample was quenched with 800 μL of MeOH), and then the mixture was vortex-mixed for 10 min at 800 rpm and centrifuged for 15 min at $3220 \times g$, 4°C ;
- 3). An aliquot of 60 μL supernatant was transferred to another

clean 96-well plate and centrifuged for 5 min at $3220 \times g$, 4 °C, then the supernatant was directly injected for LC-MS/MS analysis.

Analytical method

Instrumentation: LC-MS/MS-CB_Triple Quad 6500 plus Column: Waters
5 ACQUITY UPLC HSS T3 1.8 μm 2.1 $\times$ 50 mm

Gradient Elution; A = 0.1% Formic acid in water, B = 0.1% Formic acid in acetonitrile

Time (min)	Flow	A (%)	B (%)
0	0.6 mL/min	95	5
1	0.6 mL/min	30	70
1.2	0.6 mL/min	0	100
1.5	0.6 mL/min	0	100
1.51	0.6 mL/min	95	5
1.6	0.6 mL/min	95	5

Temperature: 45 °C

10 Injection Volume: 1.5 μl for brain, 4 μl for plasma

Ion Source: ESI+, SRM detection

Compound	MRM transition	Retention time
Example 3	306 > 147	0,82
Verapamil	455 > 165	0,97

Results

Example 3 and comparative Example 1 were formulated to 1.50 mg/mL in 10% DMSO , 5% Tween80 , 40% PG , 45% saline pH=about 7 with pH strip, clear solution and administered intravenously to male CD1 (ICR) fed mice at 3 mg/kg.

- 5
- The results are shown in the table below. Example 3 returned a plasma concentration of 292 ng/mL and a brain concentration of 61.2 ng/g at 0.5 hours after dosing. Meaning that brain to plasma concentration of 21% was observed. In contrast, comparative Example 1 returned a plasma concentration of 3087 ng/ml and a brain concentration of 5 ng/g at 0.5 hours. This means that the
- 10
- brain to plasma ratio is less than 1%.

For the treatment of CNS diseases it is advantageous to have a brain to plasma ratio value of more than 1% and preferably above 10 and 20%. Example 3 is therefore particularly useful for the treatment of CNS diseases.

Compound	Mouse plasma concentration (0.5 h) (ng/mL)	Brain homogenate concentration (0.5h) (ng/g)	Brain to plasma ratio %
Example 3	292	61.2	21
Comparative example 1	3087	5	<1

- 15
- The unbound partition coefficient (K_{puu}) was determined as a ratio between the free compound concentrations in plasma and brain:

$$K_{puu} = \frac{C_{ub,brain}}{C_{ub,plasma}}$$

Where $C_{u,brain}$ = unbound concentration in brain ($C \times F_{ub, brain}$); wherein

C = concentration at steady state; and

C_{ub,plasma} = unbound concentration in plasma (C x F_{ub}).

The K_{puu} of Comparative example 1 is thus calculated to be <0.1. This demonstrates that comparative example 1 does not effectively permeate through the blood brain barrier.

K_{puu} determination in the dog

Example 3 was loaded as a solid, Batch No. C2210502, into enteric coated capsule (0#). Fasted male beagle dog was dosed with pentagastrin (0.25 mg/mL and 0.024 mL/kg) at 6 µg/kg by intramuscular (IM) injection at approximately 30 minutes prior to administration of test compound. Capsule containing 20 mg/kg of Example 3 were administered orally and plasma and CSF samples were taken pre-dose, 0.5, 1, 2, 4, 8 12 and 24 hours post dosing and analysed for concentration of Example 3 in analogous fashion to the study above.

Results

Time (h)	Plasma concentration (ng/mL)	Time (h)	CSF concentration (ng/mL)
0	BQL*	0	BQL
0,5	1,04	0,5	BQL
1	3,20	1	BQL
2	370	2	13,7
4	5350	4	745
8	1400	8	698
12	390	12	196
24	87,1	24	27,7

*BQL: below quantification level

Analytical data

	AUC _{0-inf} (ng.h/mL)	%Fuplasma
Plasma	23816	55

CSF	6414	
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The unbound partition coefficient (K_{puu}) was determined as a ratio between the areas under the curve corrected for free compound concentrations in plasma and CSF.

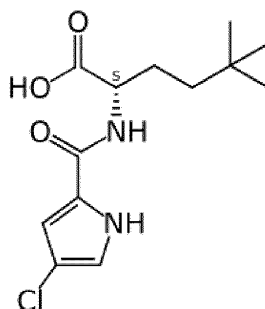
$$5 \quad K_{puu} = AUC_{0-\infty CSF} / (AUC_{0-\infty plasma} \times (\%F_{uplasma}/100))$$

$$K_{puu} = 6414 / (23816 \times (55,5/100)) = 6414 / 13218 = \mathbf{0.49}$$

Example 3 therefore has a K_{puu} of greater than 0.1, which indicates that a fraction of the unbound compound in the plasma permeates through the blood brain barrier. The compound is therefore particularly useful in the treatment of CNS diseases.

Rat K_{puu} of Comparative Example 2

Comparative Example 2 is a sortilin modulator that is not in accordance with the invention and has the following structure:



15 The K_{puu} of Comparative Example 2 in rats was determined as follows.

The compound of Comparative Example 2 was administered to the animals as a single dose either orally or intravenously. Blood samples were taken from the animals via the Saphenous vein (sv) or Vena cava (vc) at specified time points.

Terminal samples were collected under Isoflurane anaesthesia. One or two blood samples were collected in total per animal.

5 Within 30 min after sampling, the blood samples were centrifuged for plasma separation (10 min, 2700 G, RT). The samples were transferred into prelabelled plastic tubes, frozen and stored at -80°C until analysis.

Blank blood was collected via cardiac puncture under isoflurane anaesthesia to K₂EDTA syringe from animals that were not dosed with the compound of
10 Comparative Example 2. Blood was centrifuged for plasma separation (2700 G, 10 min, RT). Blank plasma was frozen and stored at -80°C until analysis.

From selected animals, brains were collected at specified time points. The animals were opened up in terminal anesthesia and the last blood sample collected from vc. For the perfusion, the heart was exposed and major veins
15 leading to the right atrium were severed. A blunt needle was then inserted into the left ventricle of the heart and approximately 30-50 ml of refrigerated saline injected to clear any remaining blood. Tissue samples were then immediately collected, frozen in liquid nitrogen and stored at -80 °C until analysis. Blank brain material was collected in the same way from animals that were not dosed with the
20 compound of Comparative Example 2.

Rat brain samples were homogenized with Omni Bead Ruptor 24 using 4-fold volume of 150 mM phosphate buffered saline (PBS, pH 7.4) per 1 part tissue (e.g. 100 mg brain tissue + 400 µl PBS).
25

The samples were prepared with protein precipitation by mixing 1 part sample (rat plasma or brain homogenate) to 3 parts of 1% formic acid in acetonitrile with internal standard cocktail (e.g. 30 µl of plasma was mixed with 90 µl of solution). Samples were mixed for 3 minutes on tabletop shaker, then centrifuged for 20
30 minutes at 2272 x g. Supernatant was transferred to analytical plate, diluted 1:1 with ultrapure water, and submitted to analysis.

Standard samples were prepared by spiking blank rat plasma and brain homogenate (5 µl standard + 45 µl blank plasma) to concentrations from 0.1 ng/ml to 20000 ng/ml of analytes.

- 5 Quality control (QC) samples were prepared by spiking blank rat plasma and brain homogenate (5 µl QC + 45 µl blank matrix) to concentrations of 0.3, 3, 30, 300 and 3000 ng/ml of the analytes in 3 replicates.

Standards and quality controls were prepared for analysis in the same way as the samples.

- 10 The brain and plasma samples were analysed by Ultra Performance Liquid Chromatography (UPLC) in tandem with Mass Spectrometry (MS) to determine the concentrations of the compound of Comparative Example 2. The K_{puu} was then calculated.

- 15 The results are shown in the tables below, for both intravenous and oral administration of the compound. The data in the tables are the average results of samples taken from two or three animals.

The data shows that the K_{puu} of Comparative Example 2 is < 0.1 and therefore this compound does not effectively permeate through the blood brain barrier.

Intravenous administration

Time sample was taken after administration of compound (h)	0.5	1	4
Nominal Dose Level (mg/kg)	1	1	1
Concentration in plasma (ng/ml)	3370	2180	1105
Concentration in brain (ng/g)	21.9	17.5	8.3

Free fraction in plasma (%)	1.2	1.2	1.2
Free fraction in brain tissue (ng/g)	9.5	9.5	9.5
Free concentration in plasma (ng/ml)	40.4	26.1	13.3
Free concentration in brain (ng/g)	2.08	1.66	0.79
K_{puu}	0.0524	0.0635	0.05925

Oral administration

Time sample was taken after administration of compound (h)	0.5	1	4
Nominal Dose Level (mg/kg)	10	10	10
Concentration in plasma (ng/ml)	13500	21800	5400
Concentration in brain (ng/g)	140.7	134.7	39.5
Free fraction in plasma (%)	1.2	1.2	1.2

Free fraction in brain tissue (ng/g)	9.5	9.5	9.5
Free concentration in plasma (ng/m)	162	262	65.9
Free concentration in brain (ng/g)	13.4	12.8	3.75
K _{puu}	0.081833	0.049	0.058333

MICRODIAYLISIS STUDY

The following experiments were performed using the compound of Example 3 as the mesylate salt.

5 Materials and Methods

In vitro experiments

In vitro experiments were performed to determine the recovery of the compound of Example 3 using MetaQuant microdialysis probes with a 4 mm exposed ethylene vinyl alcohol (EC20) membrane (CRL Groningen, the Netherlands). To this end, probes were placed in beakers containing 10 nM of the compound of Example 3 in artificial CSF (aCSF: containing 147 mM NaCl, 3.0 mM KCl, 1.2 mM CaCl₂, 1.2 mM MgCl₂ in ultrapurified H₂O). The beaker contents were continuously stirred and kept at a constant temperature of 37 °C. The probes were perfused with a slow flow of aCSF at a flow rate of 0.12 µL/min, and a carrier flow of ultrapurified H₂O at a flow rate of 0.8 µL/min. After 2 hours of prestabilization, five consecutive microdialysis samples were collected in 30-minute intervals. Samples from the beaker content were collected at the start and end of the microdialysis experiment. All samples were collected into 0.5 mL

LoBind Eppendorf tubes (Eppendorf SE, Germany; 0030108035) and stored at -80 °C until analysis.

In vivo experiments

Thirteen adult male Sprague Dawley rats were used for the experiments. Guides and push-pull microdialysis probes with a 4 mm exposed polyethersulfone (PES 200) membrane (CRL Groningen, the Netherlands) were positioned in the left hippocampus of the rats. For animals receiving test compound, guides and MetaQuant microdialysis probes with a 4 mm exposed ethylene vinyl alcohol (EC20) membrane (CRL Groningen, the Netherlands) were positioned in the right hippocampus. Coordinates for the tip of the probes were: AP = -5.3 mm (to bregma), lateral ± 4.8 mm (to midline), ventral -8.0 mm (to dura). The incisor bar was set at -3.3 mm. All coordinates were based on "The rat brain in stereotaxic coordinates" by Paxinos and Watson (2009). The probes were attached to the skull with stainless steel screws and dental cement.

For animals receiving test compound, an indwelling cannula (35 – 42 mm) was positioned in the jugular vein and exteriorized through an incision on top of the skull to allow for blood sampling. The end of each cannula was fixed in position with dental cement and attached to the skull with stainless steel screws.

The compound of Example 3 was formulated in 20% sulfobutylether- β -cyclodextrin (SBE- β -CD) in deionized water at a concentration of 20 mg/mL for oral gavage of 100 mg/kg in a volume of 5 mL/kg.

Experiments were initiated one day after probe implantation. The push-pull and MetaQuant microdialysis probes were connected with flexible PEEK tubing (Western Analytical Products Inc. USA; PK005-020) to a microperfusion pump (Harvard Apparatus, USA). Probes were perfused with artificial CSF (aCSF: containing 147 mM NaCl, 3.0 mM KCl, 1.2 mM CaCl_2 and 1.2 mM MgCl_2) at a flow rate of 0.5 $\mu\text{L}/\text{min}$ (push-pull probes) or with a slow flow of aCSF at a flow rate of 0.12 $\mu\text{L}/\text{min}$ and a carrier flow of ultrapurified H_2O at a flow rate of 0.8 $\mu\text{L}/\text{min}$ (MetaQuant probes). After two hours of prestabilization, microdialysis samples

were collected in 60-minute intervals. Three basal samples were collected. Food was removed at $t = -120$ minutes and then compound was administered at $t = 0$ minutes, and again at $t = 180$ and 360 minutes. Food was returned after the third administration. Microdialysate samples were collected for 720 minutes after the first compound administration. Samples were collected into 0.5 mL LoBind Eppendorf tubes. All samples were stored at -80°C until analysis.

During the experiment, blood samples were collected via the jugular vein catheter. Blood samples were collected into K2-EDTA collection vials and after centrifugation, resultant plasma samples were split in two aliquots in 0.5 mL LoBind Eppendorf tubes using low binding pipetting tips. All samples were stored at -80°C until analysis.

At the end of the experiment, the animals were sacrificed, and terminal brain tissue was collected for verification of probe positions.

Concentrations of the compound of Example 3 were determined by HPLC with tandem mass spectrometry (MS/MS) detection. Microdialysis samples were mixed with acetonitrile, formic acid, ultrapurified H_2O and internal standard (labetalol). Plasma samples were mixed with acetonitrile, formic acid and internal standard and subsequently centrifuged. The resultant supernatant was mixed with acetonitrile and formic acid in ultrapurified H_2O and then used for HPLC-MS analysis. An aliquot of each analytical sample was injected onto the HPLC column by an automated sample injector (Shimadzu, Japan). Chromatographic separation was performed using a Kinetex XB-C18 column ($50 \times 2.1 \text{ mm}$, $2.6 \mu\text{m}$) held at a temperature of 35°C . The mobile phases consisted of A: 0.1% formic acid in ultrapurified H_2O and B: 0.1% formic acid in acetonitrile. Elution of the compounds proceeded using a linear gradient of phases A and B at a total flow rate of 0.4 mL/min.

The MS analyses were performed using an API 4000 MS/MS system consisting of an API 4000 MS/MS detector and a Turbo Ion Spray interface (both from Applied Biosystems, The Netherlands). The acquisitions were performed in positive

ionization mode, with optimized settings for the analytes. The instruments were operated in multiple-reaction-monitoring (MRM) mode.

Suitable in-run calibration curves were fitted using weighted (1/x) regression, and the sample concentrations were determined using these calibration curves.

5 Accuracy was verified by quality control samples after each sample series. Data were calibrated and quantified using the Analyst™ data system (Applied Biosystems). MRM transitions for the analytes are shown in the table below.

Analyte	Q1	Q3
Labetalol	329.5	162.1
Example 3	306.3	117.1

10 Suitable in-run calibration curves were fitted using weighted (1/x) regression, and the sample concentrations were determined using these calibration curves. Accuracy was verified by quality control samples after each sample series. Data were calibrated and quantified using the Analyst™ data system (Applied Biosystems).

15 For the quantification of rat PGRN in study samples a commercially available ELISA kit was used (AG-45A-0043YEK-KI01, AdipoGen, Switzerland). Study samples were added to the plate in a dilution based on previous study key 2819. Plasma samples were analyzed in duplicate. Samples that were outside the detection limits were reanalyzed on another plate in a more suitable dilution. In addition, samples of which the %CV of the duplicates was above 30% were
20 reanalyzed on a different plate. Absorbance at 450 nm was measured using a Multiskan FC (ThermoFischer Scientific, USA).

Data were processed using Microsoft Excel and plotted in Prism 9 for Windows, version 9.3.1 (GraphPad Software, Inc., 1992-2021).

For evaluation of the pharmacodynamic microdialysis data, the average of the three pre-administration samples was set to 100%. If relative basal sample concentrations were <50% or >150%, they were considered to be outliers and were not used for baseline calculation. All post-administration samples were expressed as a percentage of basal level within the same subject. Prior to performing statistical analyses, outlier analyses were performed: values deviating from the relative means at a single time point within the same dose group by more than two standard deviations were excluded by a single iteration.

SigmaPlot 12.5 (Systat Software, Inc., 2011) was used for statistical analysis of the relative data. Treatment and time effects were compared between the treatment groups using two-way ANOVA for repeated measures followed by a Bonferroni post-hoc test. Treatment and time were the main factors. Main effects were evaluated only when there was no statistically significant interaction between the two main factors. In case of a significant interaction between the two factors, the main effects were not taken into account. In this case, the interaction effects were evaluated as follows:

- changes over time were evaluated for each dose comparing to levels at time point $t = 0$ minutes;
- differences in levels after the different treatments at each individual time point were compared.

The level of statistical significance was defined a priori at $p < 0.05$.

The reported microdialysate concentrations are corrected for dilutions. Correction for probe recoveries is indicated in the text where applicable.

Results

In vitro recovery of Example 3

- 5 For the MetaQuant microdialysis probe with a 4 mm exposed EC20 membrane using aCSF as perfusion fluid, relative *in vitro* recovery of Example 3 averaged $69.8 \pm 3.40\%$.

- 10 *In vitro* recovery of PGRN using a push-pull microdialysis probe with a 4 mm exposed PES 200 membrane perfused with aCSF has been previously established to be $26.9 \pm 0.86\%$ in study Key 2819B.

Histological verification

- 15 Visual assessment of the brains showed that all probes were located in the correct position.

Pharmacokinetics

- 20 Figure 1 shows the level of Example 3 in microdialysis samples from the hippocampus of adult male Sprague Dawley rats following oral administration of 100 mg/kg of Example 3 (at $t = 0, 180$ and 360 min as indicated by the arrows). At $t = -120, -60$ and 0 min, the level of Example 3 was below the lower limit of quantitation (LLOQ) of 7.31 ng/mL in microdialysate. Data are expressed as mean
25 + SEM ($n = 7$). The data has been corrected to account for 69.8% probe recovery as measured *in vitro*.

- Figure 2 shows the levels of Example 3 in plasma of adult male Sprague Dawley rats following oral administration of 100 mg/kg of Example 3 (at $t = 0, 180$ and 360 min as indicated by the arrows). At $t = -120$ min, the level of Example 3 was
30 <LLOQ of 50.0 ng/mL in plasma. Data are expressed as mean + SEM ($n = 7$).

The table below shows the basal levels of PGRN in microdialysate from the hippocampus and in plasma.

Region	Concentration (ng/mL) ± SEM	n (number of rats from which samples were taken and measured)
Hippocampus, corrected for 26.9% recovery	4.62 ± 0.41	11
Plasma	675 ± 75.3	7

5

Figure 3 shows the relative pharmacodynamic response of PGRN in hippocampal microdialysates of adult male Sprague Dawley rats following oral administration of vehicle or 100 mg/kg of Example 3 (at t = 0, 180 and 360 min as indicated by the arrows). Data are expressed as mean + SEM (n = 5 – 6 / group).

10

Pharmacodynamics

Statistical evaluation of the relative PGRN data from the hippocampus of animals treated with Example 3 by two-way ANOVA for repeated measurements demonstrated a significant interaction between treatment and time (p < 0.001). Post-hoc evaluation showed that PGRN levels in animals treated with Example 3 were elevated at t = 540 – 720 minutes when compared with t = 0 minutes. Looking at treatment within time, at t = 540 – 720 minutes, PGRN levels in animals treated with Example 3 were significantly higher than in the vehicle group. Details of the statistical analysis are shown in the table below.

20

Source of Variation	DF	SS	MS	F	p
Treatment	1	69690.402	69690.402	7.220	0.025
Animal(Treatment)	9	89633.628	9959.292		
Time	12	89764.733	7480.394	5.332	<0.001
Treatment x Time	12	54438.021	4536.502	3.234	<0.001
Residual	92	129064.821	1402.878		
Total	126	422586.580	3353.862		

Figure 4 shows the levels of PGRN in plasma of adult male Sprague Dawley rats following oral administration of 100mg/kg of Example 3 (at t = 0, 180 and 360 min as indicated by the arrows). Data are expressed as mean + SEM (n = 7).

5 Conclusions

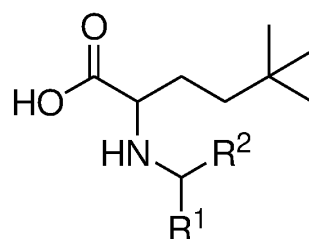
The data above demonstrates that a compound of the invention (Example 3) is able to cross the blood brain barrier following oral delivery. This surprising discovery indicates that compounds of the invention may be useful in treating disorders of the central nervous system. The data also shows that the compound of Example 3 increased the levels of PGRN in the brain of rats. This further surprising discovery suggests that compounds of the invention may have the capacity to treat conditions where an increase in PGRN in the brain may be useful. For example, the compounds of the invention may be useful in treating frontotemporal dementia, which is characterized by a depletion in the level of PGRN. Patients with depleted cerebral PGRN levels have a statistically much higher likelihood of developing frontotemporal dementia and the data presented here therefore suggests that the compounds of the invention may be useful for preventing and treating frontotemporal dementia and related conditions.

20

25

Embodiments of the Invention

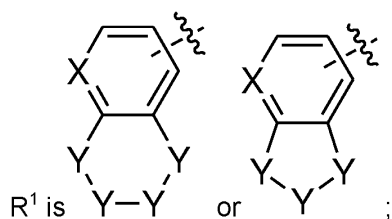
Embodiment 1. A compound of formula (I)



5

(1)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug thereof; wherein

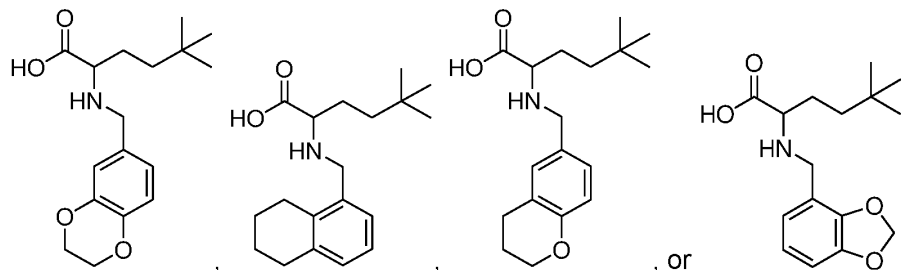


X is CR³ or N, wherein R³ is selected from the group consisting of H, halo, and C₁-C₃ alkyl;

each Y is independently CHR^4 , NR^5 , CR^6R^6 , or O, wherein R^4 is independently selected from the group consisting of H, halo, oxo, and $\text{C}_1\text{-C}_4$ alkyl; R^5 is independently selected from the group consisting of H, halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ hydroxyalkyl, $-(\text{C}_2\text{-C}_4 \text{ alkyl})\text{-O-(C}_1\text{-C}_4 \text{ alkyl)}$, $-\text{C(O)}\text{-(C}_1\text{-C}_4 \text{ alkyl)}$, and $-\text{C(O)O-(C}_1\text{-C}_4 \text{ alkyl)}$; and R^6 is independently selected from the group consisting of halo and $\text{C}_1\text{-C}_4$ alkyl;

R² is selected from the group consisting of: H, C₁-C₄ alkyl, C₂-C₄ hydroxyalkyl and C₁-C₃ haloalkyl;

wherein the compound is not one of the following compounds:



- Embodiment 2. The compound according to embodiment 1, wherein R^2 is selected from the group consisting of H, CH_3 , CH_2F , CHF_2 , and CF_3 , preferably wherein R^2 is selected from the group consisting of H, CH_3 , CHF_2 , and CF_3 .

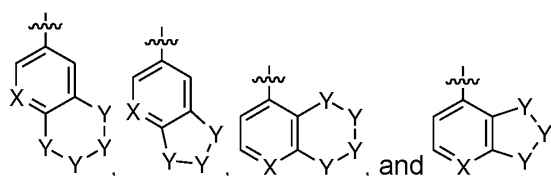
Embodiment 3. The compound according to embodiment 1 or 2, wherein each Y is independently CHR^4 , NR^5 , or O; and/or

wherein R^3 is H or C_1 - C_3 alkyl, preferably H or methyl; and/or

wherein each R^4 is independently H or oxo; and/or

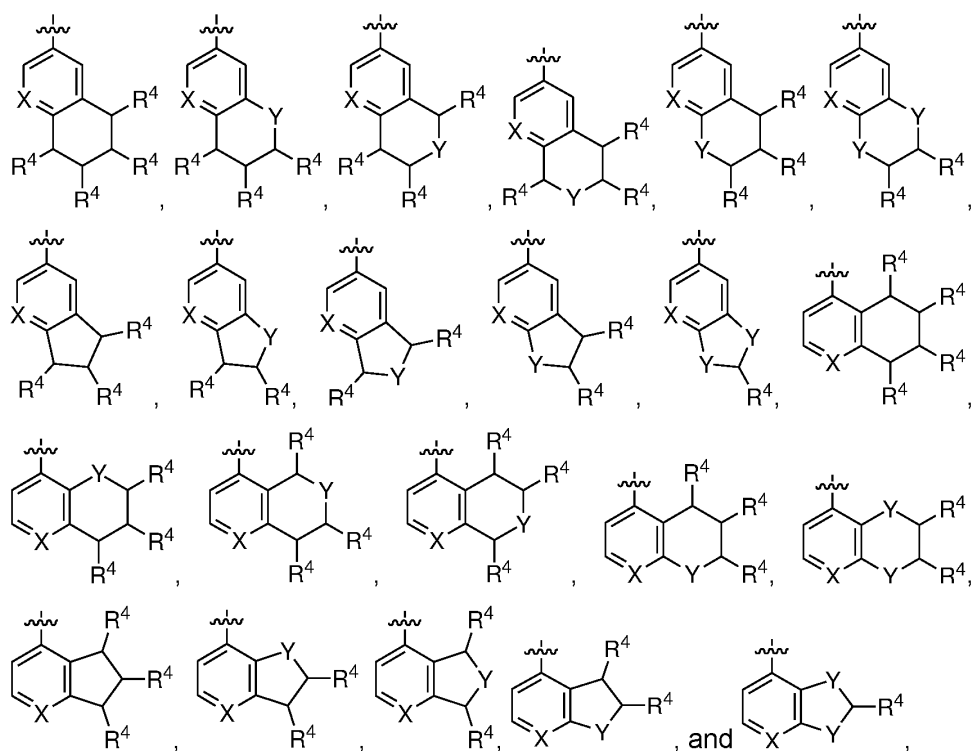
- 10 wherein each R^5 is independently H, C_1 - C_3 alkyl, or $-C(O)O-(C_1-C_4 \text{ alkyl})$, preferably H, methyl, or $-C(O)O-(\text{tert-butyl})$, more preferably H or methyl.

Embodiment 4. The compound according to any preceding embodiment, wherein R^1 is selected from one of the following groups:



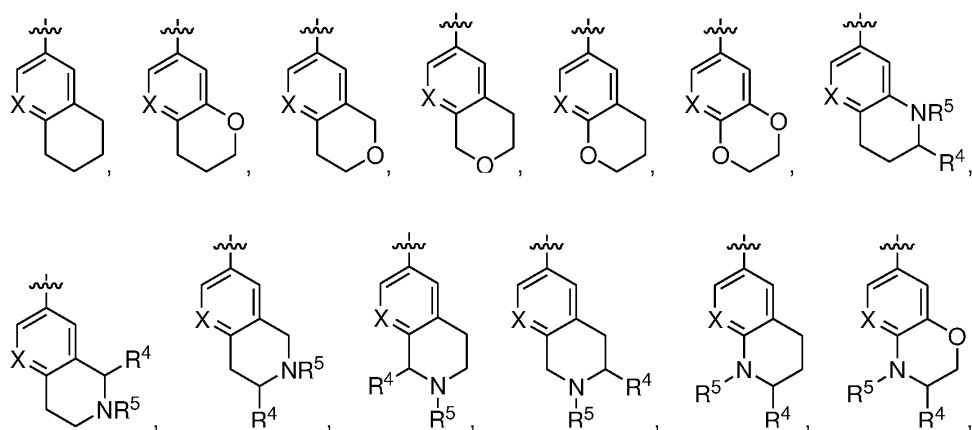
- 15 preferably wherein no more than one or two Y are NR^5 or O and the remaining Y are CHR^4 .

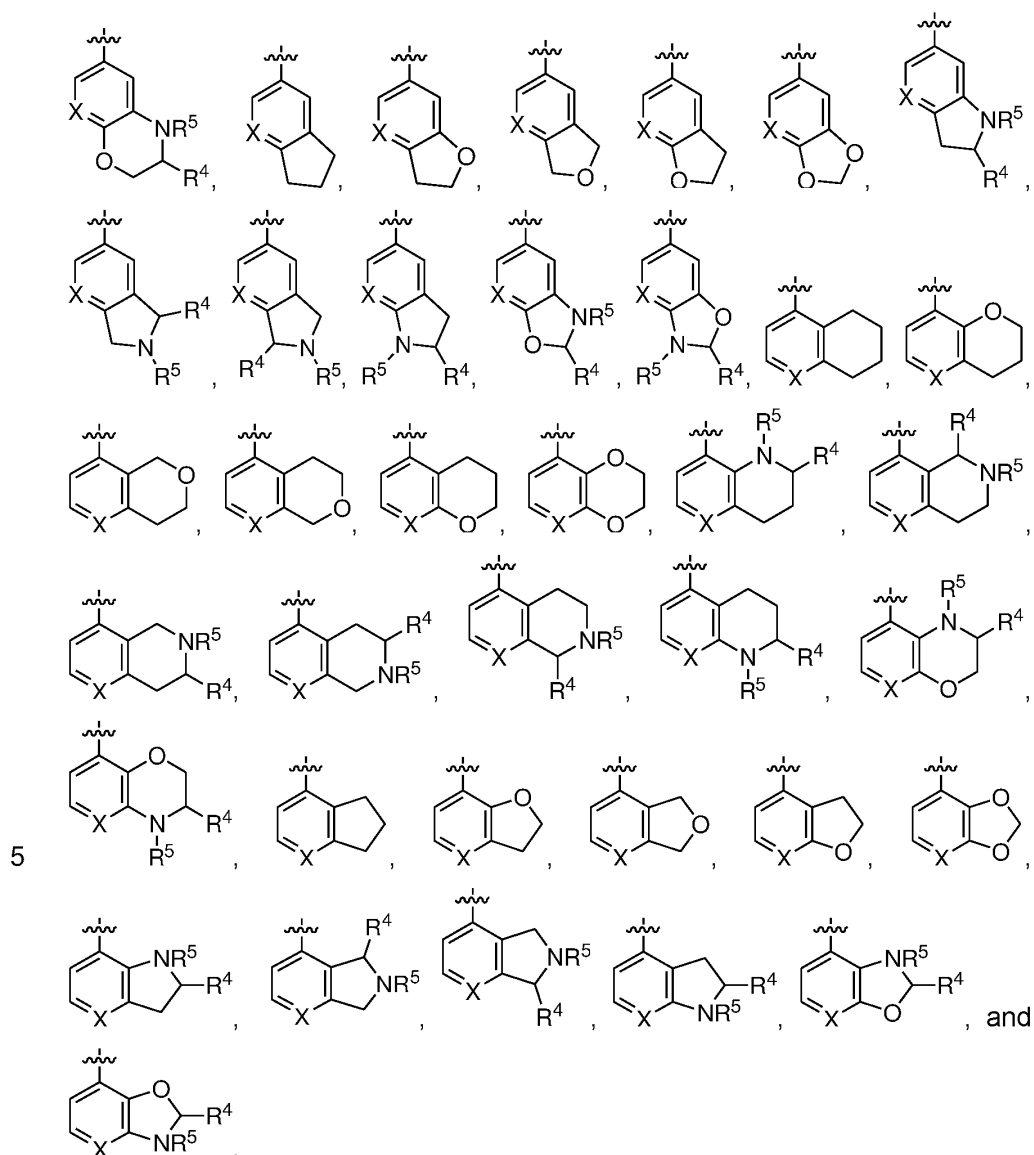
Embodiment 5. The compound according to embodiment 4, wherein R^1 is selected from one of the following groups:



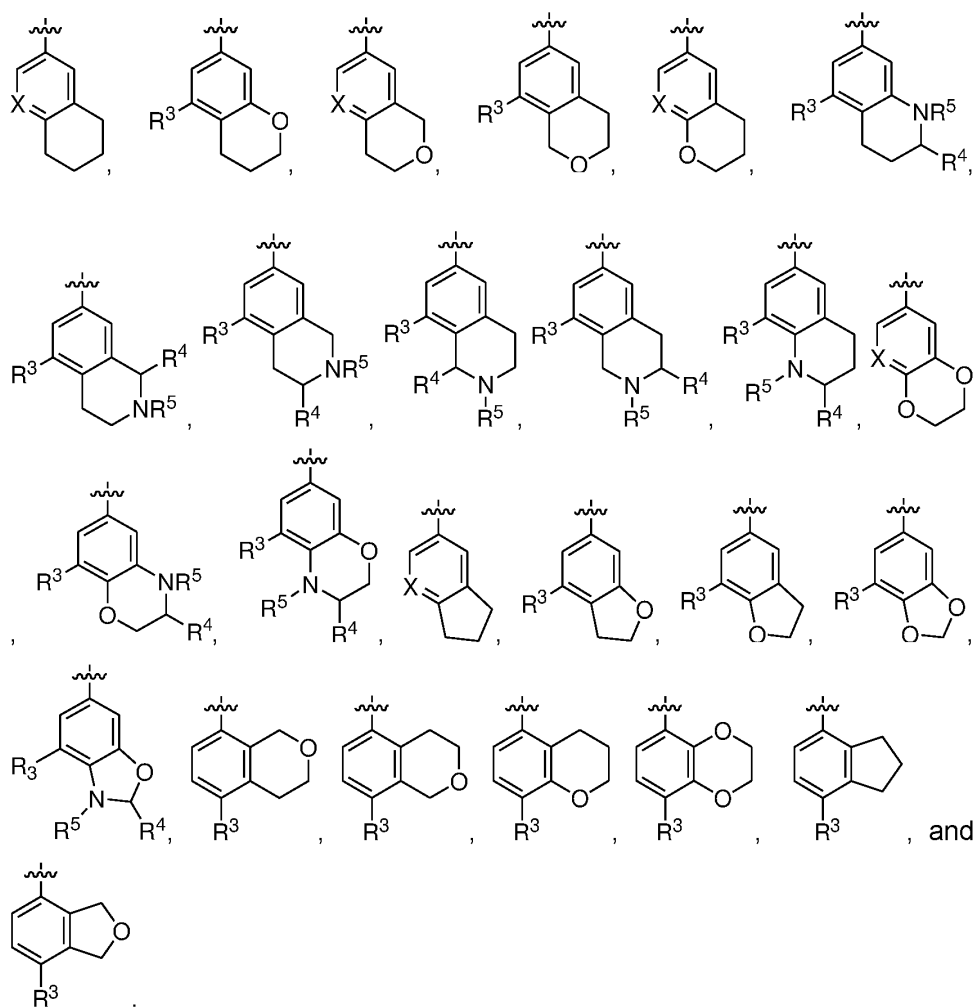
- 5 wherein each Y is independently NR^5 or O , preferably wherein one R^4 group is H or oxo and the other R^4 groups are all H .

Embodiment 6. The compound according to embodiment 5, wherein R^1 is selected from one of the following groups:

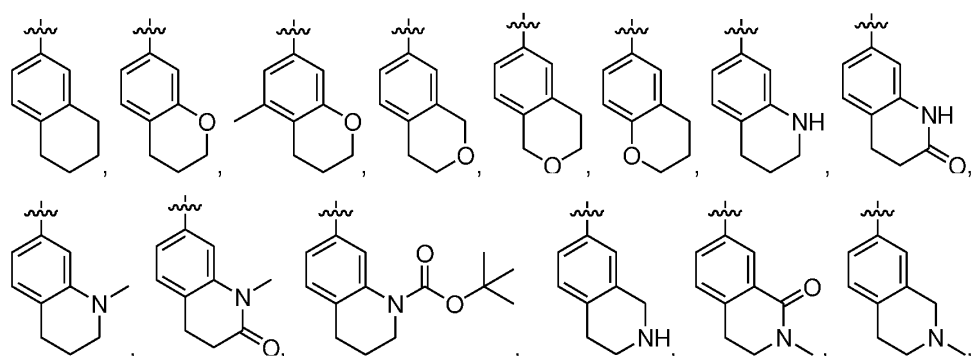


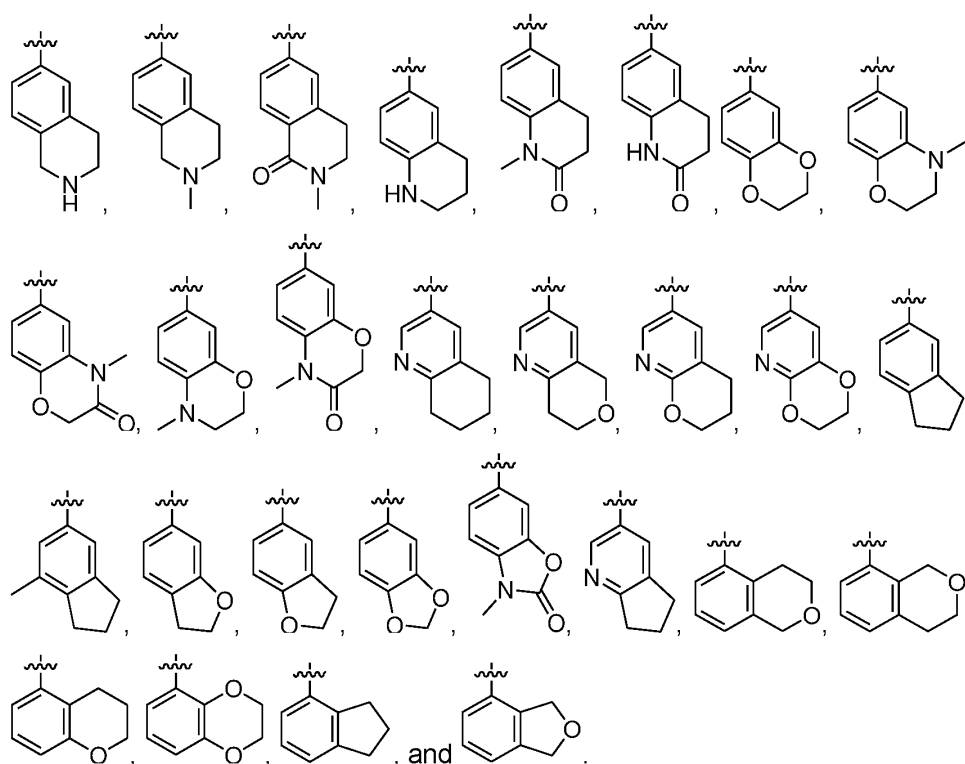


Embodiment 7. The compound according to embodiment 6, wherein R¹ is selected from one of the following groups:



Embodiment 8. The compound according to embodiment 7, wherein R¹ is selected from one of the following groups:





- 5 Embodiment 9. The compound according to any preceding embodiment, wherein
the compound is:

(2S)-2-[[[(1S)-2,2-difluoro-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino}-5,5-dimethylhexanoic acid;

(2S)-2-[(1S)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)-2,2-difluoroethyl]amino}-5,5-
10 dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[[(1R)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino]hexanoic acid;

(2S)-5,5-dimethyl-2-[(5,6,7,8-tetrahydronaphthalen-2-yl)methyl]amino}hexanoic acid;

15 (2S)-2-[[{1-[(tert-butoxy)carbonyl]-1,2,3,4-tetrahydroquinolin-7-yl}methyl)amino]-
5,5-dimethylhexanoic acid;

- (2S)-2-[(3,4-dihydro-2H-1-benzopyran-7-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[(1S)-2,2,2-trifluoro-1-(5,6,7,8-tetrahydroquinolin-3-yl)ethyl]amino}hexanoic acid;
- 5 (2S)-5,5-dimethyl-2-[(5,6,7,8-tetrahydroquinolin-3-yl)methyl]amino}hexanoic acid;
- (2S)-5,5-dimethyl-2-[(1S)-2,2,2-trifluoro-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino}hexanoic acid;
- (2S)-5,5-dimethyl-2-[(1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino}hexanoic acid;
- 10 (2S)-2-[(1R)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[(1R)-1-(1-methyl-1,2,3,4-tetrahydroquinolin-7-yl)ethyl]amino}hexanoic acid;
- 15 (2S)-2-[(1S)-1-(2,3-dihydro-1H-inden-5-yl)-2,2,2-trifluoroethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(1R)-1-(2,3-dihydro-1H-inden-5-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(1S)-1-(3,4-dihydro-2H-1-benzopyran-6-yl)ethyl]amino}-5,5-
- 20 dimethylhexanoic acid;
- (2S)-2-[(5H,6H,7H-cyclopenta[b]pyridin-3-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(2,3-dihydro-1H-inden-5-yl)methyl]amino}-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[[[4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)methyl]amino]hexanoic acid;

(2S)-2-[[[3,4-dihydro-1H-2-benzopyran-6-yl)methyl]amino]-5,5-dimethylhexanoic acid;

- 5 (2S)-5,5-dimethyl-2-[[[1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino]hexanoic acid;

(2S)-5,5-dimethyl-2-[[[5H,7H,8H-pyrano[4,3-b]pyridin-3-yl)methyl]amino]hexanoic acid;

- 10 (2S)-2-[[[3,4-dihydro-1H-2-benzopyran-7-yl)methyl]amino]-5,5-dimethylhexanoic acid;

(2S)-2-[[[(1R)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino]-5,5-dimethylhexanoic acid;

(2S)-2-[[[(1S)-1-(2,3-dihydro-1H-inden-5-yl)ethyl]amino]-5,5-dimethylhexanoic acid;

- 15 (2S)-2-[[[(1R)-1-(3,4-dihydro-2H-1-benzopyran-6-yl)ethyl]amino]-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[[[2H,3H,4H-pyrano[2,3-b]pyridin-6-yl)methyl]amino]hexanoic acid;

(2S)-2-[[[(1R)-1-(2H-1,3-benzodioxol-5-yl)ethyl]amino]-5,5-dimethylhexanoic acid;

- 20 (2S)-5,5-dimethyl-2-[[[5-methyl-3,4-dihydro-2H-1-benzopyran-7-yl)methyl]amino]hexanoic acid;

(2S)-2-[[[(1R)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)-2,2-difluoroethyl]amino]-5,5-dimethylhexanoic acid;

- (2S)-5,5-dimethyl-2-[[[(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino]hexanoic acid;
- (2S)-2-[[[(1S)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)ethyl]amino]-5,5-dimethylhexanoic acid;
- 5 (2S)-5,5-dimethyl-2-[[[(1S)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino]hexanoic acid;
- (2S)-5,5-dimethyl-2-[[[(1R)-1-(1,2,3,4-tetrahydroquinolin-7-yl)ethyl]amino]hexanoic acid;
- (2S)-2-[[[(1S)-1-(3,4-dihydro-1H-2-benzopyran-6-yl)ethyl]amino]-5,5-dimethylhexanoic acid;
- 10 (2S)-2-[[[(2H,3H-[1,4]dioxino[2,3-b]pyridin-7-yl)methyl]amino]-5,5-dimethylhexanoic acid;
- (2S)-2-[[[(1S)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino]-5,5-dimethylhexanoic acid;
- 15 (2S)-5,5-dimethyl-2-[[[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-6-yl)methyl]amino]hexanoic acid;
- (2S)-5,5-dimethyl-2-[[[(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl]amino]hexanoic acid;
- (2S)-5,5-dimethyl-2-[[[(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl]amino]hexanoic acid;
- 20 (2S)-2-[[[(2,3-dihydro-1-benzofuran-6-yl)methyl]amino]-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[[[(7-methyl-2,3-dihydro-1H-inden-5-yl)methyl]amino]hexanoic acid;

- (2S)-2-[(3,4-dihydro-1H-2-benzopyran-5-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(1R)-1-(3,4-dihydro-1H-2-benzopyran-7-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- 5 (2S)-2-[(1,3-dihydro-2-benzofuran-4-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(2,3-dihydro-1-benzofuran-5-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(3,4-dihydro-1H-2-benzopyran-8-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- 10 (2S)-2-[(2H-1,3-benzodioxol-5-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)methyl]amino}hexanoic acid;
- (2S)-2-[(1S)-1-(3,4-dihydro-1H-2-benzopyran-7-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- 15 (2S)-5,5-dimethyl-2-[(1,2,3,4-tetrahydroisoquinolin-7-yl)methyl]amino}hexanoic acid;
- (2S)-5,5-dimethyl-2-[(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]amino}hexanoic acid;
- 20 (2S)-2-[(1S)-1-(2H-1,3-benzodioxol-5-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[(1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino}hexanoic acid;
- (2S)-2-[(1R)-2,2-difluoro-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino}-5,5-dimethylhexanoic acid;

(2S)-2-[(3,4-dihydro-2H-1-benzopyran-5-yl)methyl]amino}-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]amino}hexanoic acid;

- 5 (2S)-2-[(1S)-1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]amino}-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)methyl]amino}hexanoic acid;

(2S)-2-[(2,3-dihydro-1H-inden-4-yl)methyl]amino}-5,5-dimethylhexanoic acid;

- 10 (2S)-2-[(1R)-1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]amino}-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino}hexanoic acid;

- 15 (2S)-5,5-dimethyl-2-[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino}hexanoic acid;

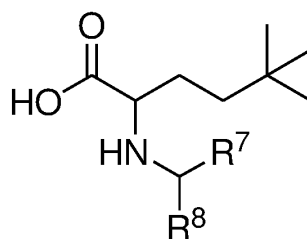
(2S)-5,5-dimethyl-2-[(1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]amino}hexanoic acid;

(2S)-5,5-dimethyl-2-[(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-7-yl)methyl]amino}hexanoic acid;

- 20 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug thereof.

Embodiment 10. A compound of formula (II)

150



(II)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug thereof; wherein

- 5 R^7 is selected from the group consisting of H, C_1 - C_3 alkyl, and C_1 - C_3 haloalkyl, preferably H, CH_3 , CHF_2 , and CF_3 , preferably H and CH_3 ; and R^8 is phenyl or pyridine, wherein phenyl and pyridine are independently substituted with one or more substituents selected from the group consisting of 5-membered heterocycloalkyl, triazolyl, -O-phenyl, and $-NR^9R^{10}$, and R^9 and R^{10} are
10 independently selected from H or C_1 - C_3 alkyl, preferably H or CH_3 , more preferably CH_3 ; or

R^7 is C_1 - C_3 hydroxyalkyl, preferably $-(C_2H_4)-OH$; and R^8 is phenyl optionally substituted with C_1 - C_3 alkoxy, preferably phenyl is optionally substituted with $-O-CH_3$.

- 15 Embodiment 11. The compound according to embodiment 10, wherein R^7 is selected from the group consisting of H, C_1 - C_3 alkyl, and C_1 - C_3 haloalkyl, and R^8 is phenyl substituted with pyrrolidinyl, triazolyl, -O-phenyl, or $-NR^9R^{10}$, or R^8 is pyridine substituted with -O-phenyl; or

- wherein R^7 is C_1 - C_3 hydroxyalkyl and R^8 is phenyl optionally substituted with
20 C_1 - C_3 alkoxy.

Embodiment 12. The compound according to embodiment 10 or 11, wherein the compound is

(2S)-5,5-dimethyl-2-[[[(2-phenoxy)pyridin-4-yl)methyl]amino]hexanoic acid;

- (2S)-5,5-dimethyl-2-[[[6-phenoxy-3-pyridinyl]methyl]amino]hexanoic acid;
- (2S)-5,5-dimethyl-2-[[[3-(pyrrolidin-1-yl)phenyl]methyl]amino]hexanoic acid;
- 2-[[[1S]-3-hydroxy-1-phenylpropyl]amino]-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[[[1R]-1-(6-phenoxy-3-pyridinyl)ethyl]amino]hexanoic acid;
- 5 (2S)-5,5-dimethyl-2-[[[1S]-1-(6-phenoxy-3-pyridinyl)ethyl]amino]hexanoic acid;
- (2S)-5,5-dimethyl-2-[[[4-phenoxyphenyl]methyl]amino]hexanoic acid;
- (2S)-2-[[[3-(dimethylamino)phenyl]methyl]amino]-5,5-dimethylhexanoic acid;
- (2S)-2-[[[1R]-3-hydroxy-1-(3-methoxyphenyl)propyl]amino]-5,5-dimethylhexanoic acid;
- 10 (2S)-5,5-dimethyl-2-[[[3-phenoxyphenyl]methyl]amino]hexanoic acid;
- (2S)-2-[[[1S]-3-hydroxy-1-(3-methoxyphenyl)propyl]amino]-5,5-dimethylhexanoic acid;
- (2S)-2-[[[1R]-3-hydroxy-1-phenylpropyl]amino]-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[[[3-(1H-1,2,4-triazol-1-yl)phenyl]methyl]amino]hexanoic acid;
- 15 acid;
- or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug thereof.
- Embodiment 13.A pharmaceutical composition comprising a compound according to any preceding embodiment and a pharmaceutically acceptable carrier, excipient, and/or diluent.
- 20 Embodiment 14. The compound according to any one of embodiments 1 to 12, or the pharmaceutical composition of embodiment 13, for use in therapy.

Embodiment 15. The compound according to any one of embodiments 1 to 12, or the pharmaceutical composition of embodiment 13, for use in the treatment or prevention of a neurodegenerative disorder, a psychiatric disorder, an inflammatory disorder, a cancer, pain, diabetes mellitus, diabetic retinopathy, glaucoma, uveitis, cardiovascular diseases, kidney disease, psoriasis, hereditary eye conditions, hearing loss or diseases characterized by misfolded tau;

wherein the neurodegenerative disorder is preferably selected from motor neuron diseases, Frontotemporal Lobar Degeneration (FTLD), frontotemporal dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion diseases such as Creutzfeldt-Jakob disease (CJD), acute brain injury, spinal cord injury and stroke, preferably wherein the motor neuron disease is selected from amyotrophic lateral sclerosis (ALS), Primary Lateral Sclerosis, and Progressive Muscular Atrophy;

wherein the neurodegenerative disorder is preferably a neurodegenerative disorder characterised by misfolded TAR DNA-binding protein 43, such as amyotrophic lateral sclerosis, Alzheimer's disease, Frontotemporal Lobar Degeneration, or frontotemporal dementia;

wherein the psychiatric disorder is preferably selected from bipolar disorder, major depression, post-traumatic stress disorder, and anxiety disorders;

wherein the inflammatory disorder is preferably selected from inflammatory diseases and neuroinflammation;

wherein the cancer is preferably selected from breast cancer, lung cancer, ovarian cancer, prostate cancer, thyroid cancer, pancreatic cancer, glioblastoma and colorectal cancer;

wherein the cardiovascular disease is preferably selected from atherosclerosis, cardiomyopathy, heart attack, arrhythmias, heart failure, and ischemic heart disease; and

wherein the hearing loss is preferably selected from noise-induced hearing loss, ototoxicity induced hearing loss, age-induced hearing loss, idiopathic hearing loss, tinnitus and sudden hearing loss.

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Sequences referenced throughout the specification and forming part of the description

SEQ ID NO: 1 (full length sortilin- isoform 1)

5 1 MERPWGAADG LSRWPHGLGL LLLLQLLPPS TLSQDRLDAP PPPAAPLPRW
51 SGPIGVSWGL RAAAAGGAFP RGGRWRRSAP GEDEECGRVR Dfvaklannt
101 HQHVFDLRLG SVSLSWWGDS TGVILVLTTF HVPLVIMTFG QSKLYRSEDY
151 GKNFKDITDL INNTFIRTEF GMAIGPENSG KVVLTAEVSG GSRGGRIFRS
201 SDFAKNFVQT DLPFHPLTQM MYSPQNSDYL LALSTENGLW VSKNFGGKWE
10 251 EIHKAVCLAK WGS DN TIFFT TYANGSCKAD LGAL ELWRTS DLGKSFKTIG
301 VKIYSFGLGG RFLFASVMAD KDTTRRIHVS TDQGD TWSMA QLPSVGQE QF
351 YSILAANDDM VFMHVDEPGD TGF GTIFTSD DRGIVYSKSL DRHLYTTTGG
401 ETDFTNVTSL RGVYITSVLS EDNSIQTMIT FDQGGRWTHL RKPENSECDA
451 TAKNKNECSL HIHASYSISQ KLNVP MAPLS EPNAV GIVIA HGSVGD AISV
15 501 MVPDVYISDD GGYSWTKMLE GPHYYTILDS GGIIV AIEHS SRPINVIKFS
551 TDEGQCWQTY TFRDPIYFT GLASEPGARS MNISIWGFTE SFLTSQWWSY
601 TIDFKDILER NCEEKDYTIW LAHSTDPE DY EDGCILGYKE QFLRLRKSSM
651 CQNGRDYVVT KQPSICLCSL EDFLCDFGY Y RPENDSKC VE QPELKGHDLE
701 FCLYGREEHL TTNGYRKIPG DKCQGGVNPV REVKDLKKKC TSNFLSPEKQ
20 751 NSKNSNVPII LAIVGLMLVT VVAGVLIVKK YVCGGRFLVH RYSVLQQHAE
801 ANGVDGVDAL DTASHTNKSG YHDDSD EDLL E

SEQ ID NO: 2 (full length sortilin- isoform 2)

25 1 MERPWGAADG LSRWPHGLGL LLLLQLLPPS TLSQDRLDAP PPPAAPLPRW
51 SGPIGVSWGL RAAAAGGAFP RGGRWRRSAP GEDEECGRVR Dfvaklannt
101 HQHVFDLRLG SVSLSWWGDS TGVILVLTTF HVPLVIMTFG QSKLYRSEDY
151 GKNFKDITDL INNTFIRTEF GMAIGPENSG KVVLTAEVSG GSRGGRIFRS
201 SDFAKNFVQT DLPFHPLTQM MYSPQNSDYL LALSTENGLW VSKNFGGKWE
30 251 EIHKAVCLAK WGS DN TIFFT TYANGSCTDL GALELWRTSD LGKSFKTIGV
301 KIYSFGLGGR FLFASVMADK DTTRRIHVST DQGD TWSMAQ LPSVGQE QFY
351 SILAANDDMV FMHVDEPGDT GFGTIFTSDD RGIVYSKSLD RHLYTTTGG E
401 TDFTNVTSLR GVIYTSVLSE DNSIQTMITF DQGGRWTHLR KPENSECDAT
451 AKNKNECSLH IHASYSISQK LNVPMAPLSE PNAV GIVIAH GSVGD AISVM
35 501 VPDVYISDDG GYSWTKMLEG PHYYTILDSG GIIV AIEHSS RPINVIKFS
551 DEGQCWQTYT FTRDPIYFTG LASEPGARSM NISIWGFTE SFLTSQWWSYT

601 IDFKDILERN CEEKDYTIWL AHSTDPEDYE DGCILGYKEQ FLRLRKSSVC
651 QNGRDYVVTQ QPSICLCSLE DFLCDFGYR PENDSKCVEQ PELKGHDLEF
701 CLYGREEHLT TNGYRKIPGD KCQGGVNPVR EVKDLKKKCT SNFLSPEKQN
751 SKSNSVPIIL AIVGLMLVTV VAGVLIVKKY VCGGRFLVHR YSVLQQHAEA
5 801 NGVDGVDALD TASHTNKSGY HDDSDEDLLE

SEQ ID NO: 3 (mature sortilin)

1 MTFGQSKLYR SEDYGKNFKD ITDLINNTFI RTEFGMAIGP ENSGKVVLT
10 51 EVSGGSRGGR IFRSSDFAKN FVQTDLPFHP LTQMMYSPQN SDYLLALSTE
101 NGLWWSKNFG GKWEEIHKAV CLAKWGSNT IFFTTYANGS CTDLGALELW
151 RTSDLGKSFK TIGVKIYSFG LGGRFLFASV MADKDTTRRI HVSTDQGDW
201 SMAQLPSVGQ EQFYSILAAN DDMVFMHVDE PGDTGFGTIF TSDDRIGIVYS
251 KSLDRHLYTT TGGETDFTNV TSLRGVYITS VLSEDNSIQT MITFDQGGRW
15 301 THLRKPENSE CDATEKNKNE CSLHIHASYS ISQKLNVPMA PLSEPNAVGI
361 VIAHGSVGDA ISVMVPDVYI SDDGGYSWTK MLEGPYHYTI LDSGGIIVAI
401 EHSSRPINVI KFSTDEGQCW QTYTFTDPYI YFTGLASEPG ARSMNISIWG
451 FTESFLTSQW VSYTIDFKDI LERNCEEKDY TIWLAHSTDP EDYEDGCILG
501 YKEQFLRLRK SSVCQNGRDY VVTQPSICL CSLEDFLCDF GYRPENDSK
20 551 CVEQPELKGH DLEFCLYGRE EHLTTNGYRK IPGDKCQGGV NPVREVKDLK
601 KKCTSNFLSP EKQNSKNSV PIILAIVGLM LVTVVAGVLI VKKYVCGGRF
651 LVHRYSVLQQ HAEANGVDGV DALDTASHTN KSGYHDDSDE DLLE

25 SEQ ID NO: 4 (Murine Sortilin)

>sp|Q6PHU5|SORT_MOUSE Sortilin OS=Mus musculus OX=10090 GN=Sort1 PE=1 SV=1

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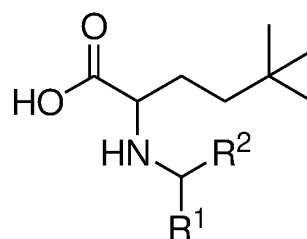
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G

30 VILVLTTFQVPLVIVSFGQSKLYRSEDYGKNFKDITNLINNTFIRTEFGMAIGPENSGKV
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NAVGIIVAHGSGDAISVMVPDVYISDDGGYSWAKMLEGPHYTTILDSGGIIVAEHSNR
PINVIKFSTDEGQCWQSYVFTQEPIYFTGLASEPGARSMNISIWGFTESFITRQWWSYTV
5 DFKDILERNCEEDDYTTWLAHSTDPGDYKDGILGYKEQFLRLRKSSVCQNGRDYVVAQK
PSVCPCSLEDFLCDFGYFRPENASECVEQPELKGHELEFCLYGKEEHLTTNGYRKIPGDK
CQGGMNPAREVKDLKKKCTSNFLNPTKQNSKSNVPIILAIVGLMLVTVAGVLIVKKYV
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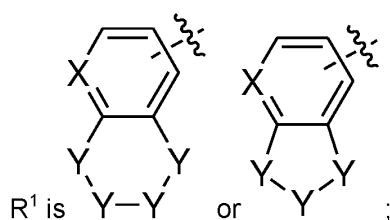
CLAIMS

1. A compound of formula (I)



(I)

- 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug thereof; wherein



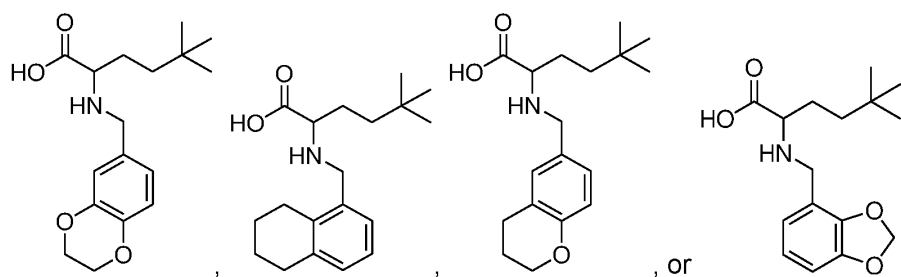
X is CR³ or N, wherein R³ is selected from the group consisting of H, halo, and C₁-C₃ alkyl;

- 10 each Y is independently CHR⁴, NR⁵, CR⁶R⁶, C(O), or O, wherein R⁴ is independently selected from the group consisting of H, halo, and C₁-C₄ alkyl; R⁵ is independently selected from the group consisting of H, halo, C₁-C₄ alkyl, C₂-C₄ hydroxyalkyl, -(C₂-C₄ alkyl)-O-(C₁-C₄ alkyl), -C(O)-(C₁-C₄ alkyl), and -C(O)O-(C₁-C₄ alkyl); and R⁶ is independently selected from the group
 15 consisting of halo and C₁-C₄ alkyl;

R² is selected from the group consisting of: H, C₁-C₄ alkyl, C₂-C₄ hydroxyalkyl and C₁-C₃ haloalkyl;

wherein the compound is not one of the following compounds:

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2. The compound according to claim 1, wherein R^2 is selected from the group consisting of H, CH_3 , CH_2F , CHF_2 , and CF_3 , preferably wherein R^2 is selected from the group consisting of H, CH_3 , CHF_2 , and CF_3 .

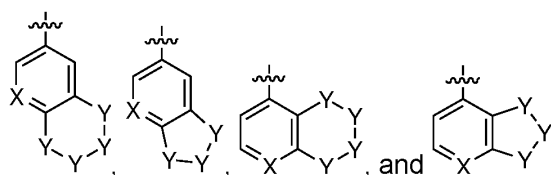
5 3. The compound according to claim 1 or 2, wherein each Y is independently CHR^4 , NR^5 , $C(O)$, or O; and/or

wherein R^3 is H or C_1 - C_3 alkyl, preferably H or methyl; and/or

wherein each R^4 is H; and/or

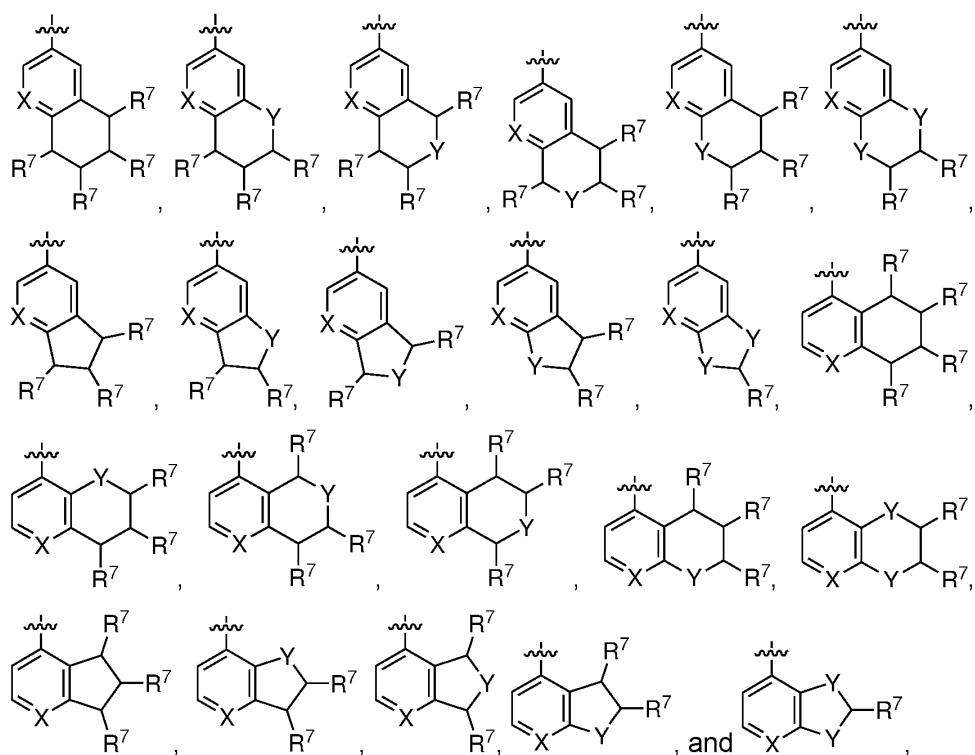
10 wherein each R^5 is independently H, C_1 - C_3 alkyl, or $-C(O)O-(C_1-C_4 \text{ alkyl})$, preferably H, methyl, or $-C(O)O-(\text{tert-butyl})$, more preferably H or methyl.

4. The compound according to any preceding claim, wherein R^1 is selected from one of the following groups:

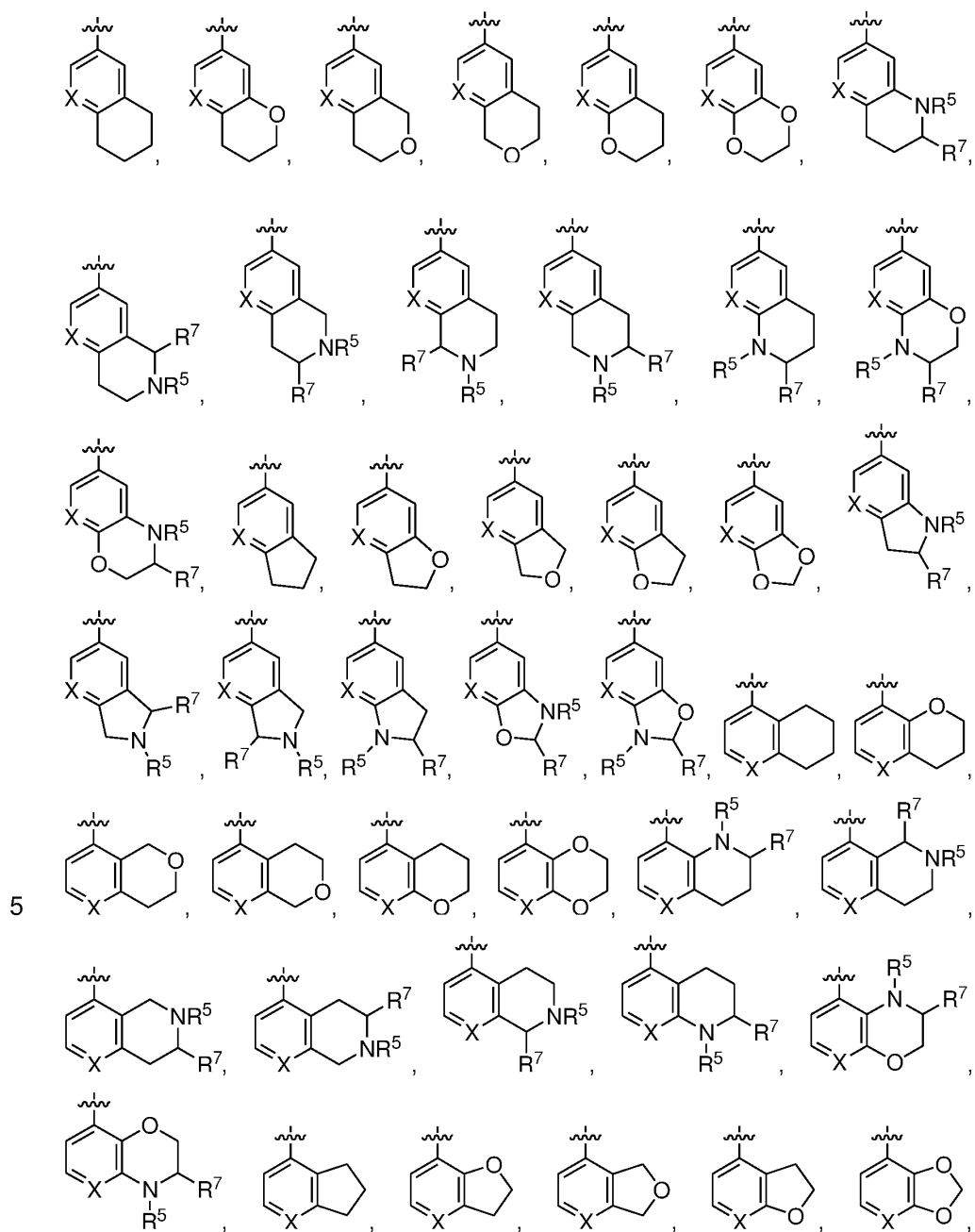


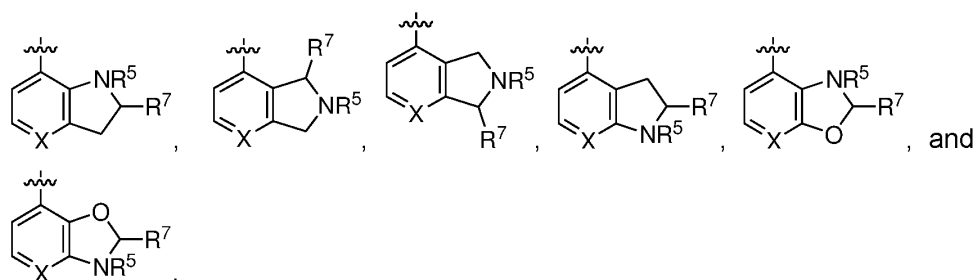
15 preferably wherein no more than one or two Y are NR^5 or O and the remaining Y are independently $C(O)$ or CHR^4 .

5. The compound according to claim 4, wherein R^1 is selected from one of the following groups:

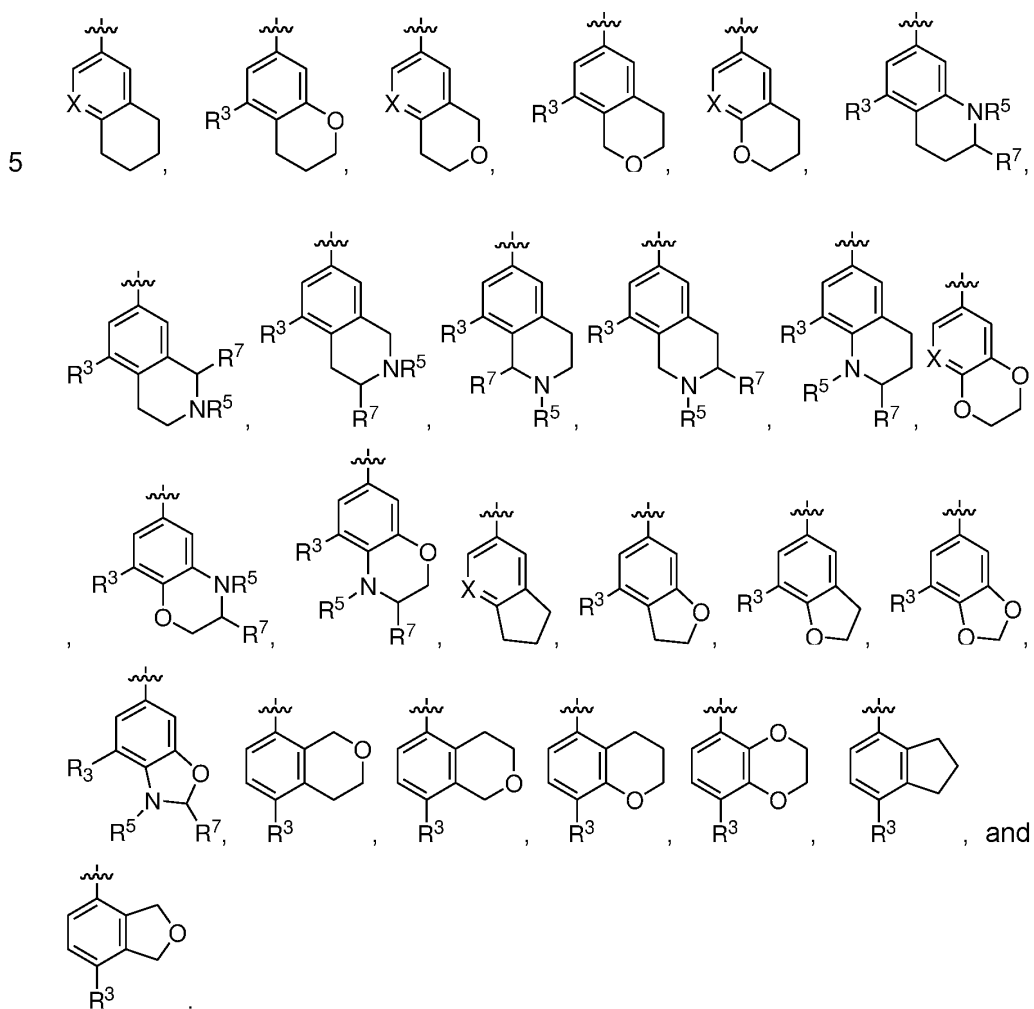


- 5 wherein each Y is independently NR^5 or O, and each R^7 is independently selected from the group consisting of H, halo, and $\text{C}_1\text{-C}_4$ alkyl or the R^7 together with the carbon atom to which it is attached forms an oxo group, preferably wherein each R^7 is H or the R^7 together with the carbon atom to which it is attached forms an oxo group, more preferably wherein one R^7 group is H or the R^7 group together with the carbon atom to which it is attached forms an oxo group, and the other R^7 groups are all H.
- 10
6. The compound according to claim 5, wherein R^1 is selected from one of the following groups:

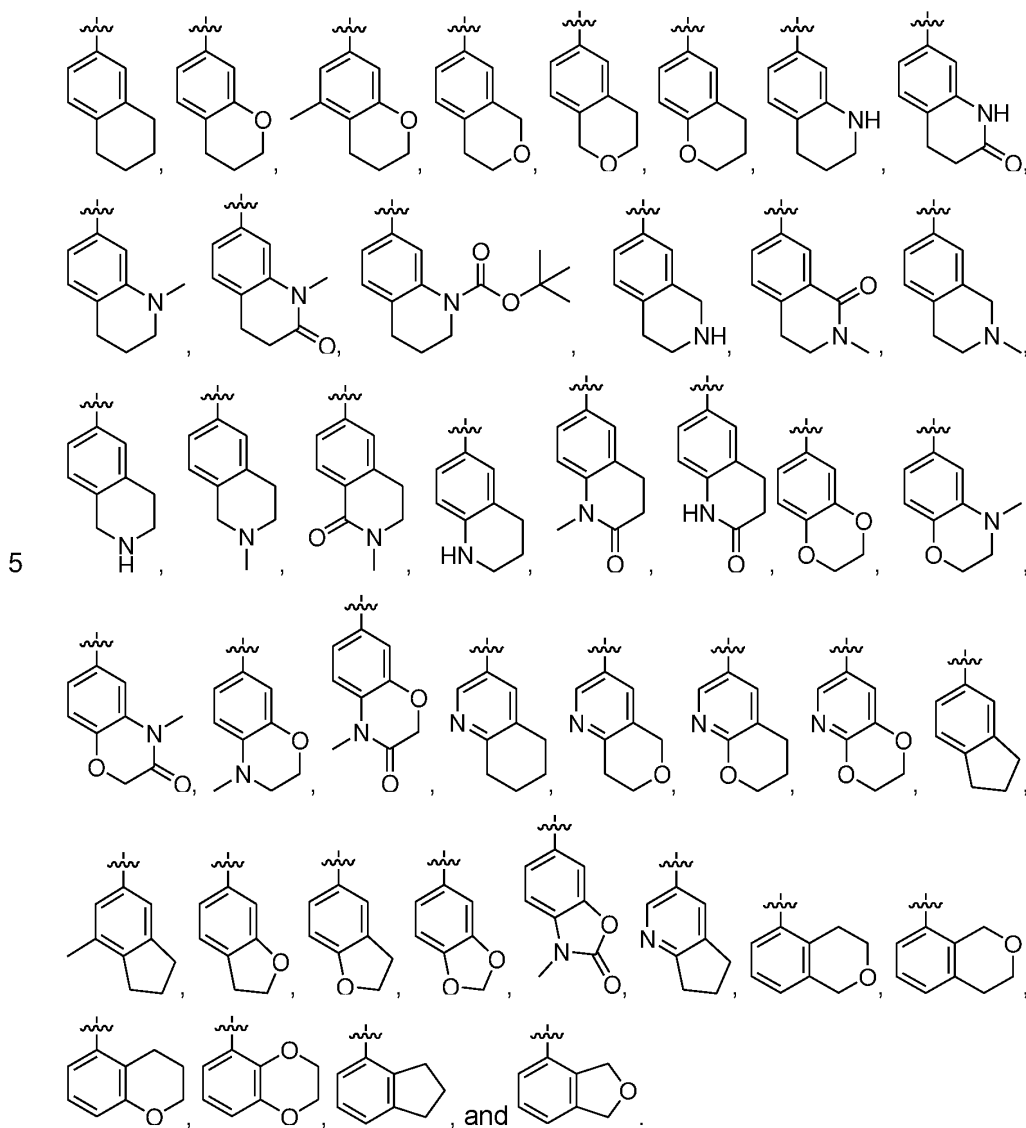




7. The compound according to claim 6, wherein R^1 is selected from one of the following groups:



8. The compound according to claim 7, wherein R¹ is selected from one of the following groups:



9. The compound according to any preceding claim, wherein the compound is:

10

(2S)-2-[(1S)-2,2-difluoro-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino}-5,5-dimethylhexanoic acid;

- (2S)-2-[[[(1S)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)-2,2-difluoroethyl]amino]-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[[[(1R)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino]hexanoic acid;
- 5 (2S)-5,5-dimethyl-2-[[[(5,6,7,8-tetrahydronaphthalen-2-yl)methyl]amino]hexanoic acid;
- (2S)-2-[[{1-[(tert-butoxy)carbonyl]-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino]-5,5-dimethylhexanoic acid;
- (2S)-2-[[[(3,4-dihydro-2H-1-benzopyran-7-yl)methyl]amino]-5,5-dimethylhexanoic acid;
- 10 (2S)-5,5-dimethyl-2-[[[(1S)-2,2,2-trifluoro-1-(5,6,7,8-tetrahydroquinolin-3-yl)ethyl]amino]hexanoic acid;
- (2S)-5,5-dimethyl-2-[[[(5,6,7,8-tetrahydroquinolin-3-yl)methyl]amino]hexanoic acid;
- 15 (2S)-5,5-dimethyl-2-[[[(1S)-2,2,2-trifluoro-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino]hexanoic acid;
- (2S)-5,5-dimethyl-2-[[[(1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino]hexanoic acid;
- (2S)-2-[[[(1R)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)ethyl]amino]-5,5-dimethylhexanoic acid;
- 20 (2S)-5,5-dimethyl-2-[[[(1R)-1-(1-methyl-1,2,3,4-tetrahydroquinolin-7-yl)ethyl]amino]hexanoic acid;
- (2S)-2-[[[(1S)-1-(2,3-dihydro-1H-inden-5-yl)-2,2,2-trifluoroethyl]amino]-5,5-dimethylhexanoic acid;

- (2S)-2-[(1R)-1-(2,3-dihydro-1H-inden-5-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(1S)-1-(3,4-dihydro-2H-1-benzopyran-6-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- 5 (2S)-2-[(5H,6H,7H-cyclopenta[b]pyridin-3-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(2,3-dihydro-1H-inden-5-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl)methyl]amino}hexanoic acid;
- 10 (2S)-2-[(3,4-dihydro-1H-2-benzopyran-6-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino}hexanoic acid;
- (2S)-5,5-dimethyl-2-[(5H,7H,8H-pyrano[4,3-b]pyridin-3-yl)methyl]amino}hexanoic acid;
- 15 (2S)-2-[(3,4-dihydro-1H-2-benzopyran-7-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(1R)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- 20 (2S)-2-[(1S)-1-(2,3-dihydro-1H-inden-5-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(1R)-1-(3,4-dihydro-2H-1-benzopyran-6-yl)ethyl]amino}-5,5-dimethylhexanoic acid;

- (2S)-5,5-dimethyl-2-[(2H,3H,4H-pyrano[2,3-b]pyridin-6-yl)methyl]amino}hexanoic acid;
- (2S)-2-[(1R)-1-(2H-1,3-benzodioxol-5-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[(5-methyl-3,4-dihydro-2H-1-benzopyran-7-yl)methyl]amino}hexanoic acid;
- 5 (2S)-2-[(1R)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)-2,2-difluoroethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[(2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)methyl]amino}hexanoic acid;
- 10 (2S)-2-[(1S)-1-(3,4-dihydro-2H-1-benzopyran-7-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[(1S)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino}hexanoic acid;
- (2S)-5,5-dimethyl-2-[(1R)-1-(1,2,3,4-tetrahydroquinolin-7-yl)ethyl]amino}hexanoic acid;
- 15 (2S)-2-[(1S)-1-(3,4-dihydro-1H-2-benzopyran-6-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-2-[(2H,3H-[1,4]dioxino[2,3-b]pyridin-7-yl)methyl]amino}-5,5-dimethylhexanoic acid;
- 20 (2S)-2-[(1S)-1-(2,3-dihydro-1,4-benzodioxin-6-yl)ethyl]amino}-5,5-dimethylhexanoic acid;
- (2S)-5,5-dimethyl-2-[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-6-yl)methyl]amino}hexanoic acid;

(2S)-5,5-dimethyl-2-[[[(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl]amino]hexanoic acid;

(2S)-5,5-dimethyl-2-[[[(2-methyl-1,2,3,4-tetrahydroisoquinolin-7-yl)methyl]amino]hexanoic acid;

- 5 (2S)-2-[[[(2,3-dihydro-1-benzofuran-6-yl)methyl]amino]-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[[[(7-methyl-2,3-dihydro-1H-inden-5-yl)methyl]amino]hexanoic acid;

- 10 (2S)-2-[[[(3,4-dihydro-1H-2-benzopyran-5-yl)methyl]amino]-5,5-dimethylhexanoic acid;

(2S)-2-[[[(1R)-1-(3,4-dihydro-1H-2-benzopyran-7-yl)ethyl]amino]-5,5-dimethylhexanoic acid;

(2S)-2-[[[(1,3-dihydro-2-benzofuran-4-yl)methyl]amino]-5,5-dimethylhexanoic acid;

- 15 (2S)-2-[[[(2,3-dihydro-1-benzofuran-5-yl)methyl]amino]-5,5-dimethylhexanoic acid;

(2S)-2-[[[(3,4-dihydro-1H-2-benzopyran-8-yl)methyl]amino]-5,5-dimethylhexanoic acid;

(2S)-2-[[[(2H-1,3-benzodioxol-5-yl)methyl]amino]-5,5-dimethylhexanoic acid;

- 20 (2S)-5,5-dimethyl-2-[[[(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)methyl]amino]hexanoic acid;

(2S)-2-[[[(1S)-1-(3,4-dihydro-1H-2-benzopyran-7-yl)ethyl]amino]-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[[[(1,2,3,4-tetrahydroisoquinolin-7-yl)methyl]amino]hexanoic acid;

(2S)-5,5-dimethyl-2-[[[(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]amino]hexanoic acid;

- 5 (2S)-2-[[[(1S)-1-(2H-1,3-benzodioxol-5-yl)ethyl]amino]-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[[[(1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino]hexanoic acid;

(2S)-2-[[[(1R)-2,2-difluoro-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl]amino]-5,5-dimethylhexanoic acid;

- 10 (2S)-2-[[[(3,4-dihydro-2H-1-benzopyran-5-yl)methyl]amino]-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[[[(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]amino]hexanoic acid;

- 15 (2S)-2-[[[(1S)-1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]amino]-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[[[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)methyl]amino]hexanoic acid;

(2S)-2-[[[(2,3-dihydro-1H-inden-4-yl)methyl]amino]-5,5-dimethylhexanoic acid;

- 20 (2S)-2-[[[(1R)-1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]amino]-5,5-dimethylhexanoic acid;

(2S)-5,5-dimethyl-2-[[[(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino]hexanoic acid;

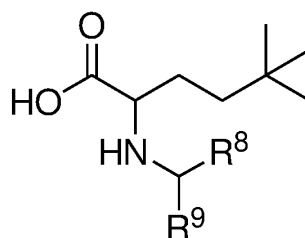
(2S)-5,5-dimethyl-2-[[[(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)methyl]amino]hexanoic acid;

(2S)-5,5-dimethyl-2-[[(1,2,3,4-tetrahydroisoquinolin-6-yl)methyl]amino]hexanoic acid;

(2S)-5,5-dimethyl-2-[[(4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-7-yl)methyl]amino]hexanoic acid;

- 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug thereof.

10. A compound of formula (II)



(II)

- 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug thereof; wherein

R⁸ is selected from the group consisting of H, C₁-C₃ alkyl, and C₁-C₃ haloalkyl, preferably H, CH₃, CHF₂, and CF₃, preferably H and CH₃; and R⁹ is phenyl or pyridine, wherein phenyl and pyridine are independently substituted with one or
 15 more substituents selected from the group consisting of 5-membered heterocycloalkyl, triazolyl, -O-phenyl, and -NR¹⁰R¹¹, and R¹⁰ and R¹¹ are independently selected from H or C₁-C₃ alkyl, preferably H or CH₃, more preferably CH₃; or

- R⁸ is C₁-C₃ hydroxyalkyl, preferably -(C₂H₄)-OH; and R⁹ is phenyl optionally
 20 substituted with C₁-C₃ alkoxy, preferably phenyl is optionally substituted with -O-CH₃.

11. The compound according to claim 10, wherein R⁸ is selected from the group consisting of H, C₁-C₃ alkyl, and C₁-C₃ haloalkyl, and R⁹ is phenyl

substituted with pyrrolidinyl, triazolyl, -O-phenyl, or -NR¹⁰R¹¹, or R⁹ is pyridine substituted with -O-phenyl; or

wherein R⁸ is C₁-C₃ hydroxyalkyl and R⁹ is phenyl optionally substituted with C₁-C₃ alkoxy.

- 5 12. The compound according to claim 10 or 11, wherein the compound is
- (2S)-5,5-dimethyl-2-([(2-phenoxy pyridin-4-yl)methyl]amino)hexanoic acid;
- (2S)-5,5-dimethyl-2-([(6-phenoxy pyridin-3-yl)methyl]amino)hexanoic acid;
- (2S)-5,5-dimethyl-2-([(3-(pyrrolidin-1-yl)phenyl)methyl]amino)hexanoic acid;
- 2-([(1S)-3-hydroxy-1-phenylpropyl]amino)-5,5-dimethylhexanoic acid;
- 10 (2S)-5,5-dimethyl-2-([(1R)-1-(6-phenoxy pyridin-3-yl)ethyl]amino)hexanoic acid;
- (2S)-5,5-dimethyl-2-([(1S)-1-(6-phenoxy pyridin-3-yl)ethyl]amino)hexanoic acid;
- (2S)-5,5-dimethyl-2-([(4-phenoxyphenyl)methyl]amino)hexanoic acid;
- (2S)-2-([(3-(dimethylamino)phenyl)methyl]amino)-5,5-dimethylhexanoic acid;
- (2S)-2-([(1R)-3-hydroxy-1-(3-methoxyphenyl)propyl]amino)-5,5-dimethylhexanoic
- 15 acid;
- (2S)-5,5-dimethyl-2-([(3-phenoxyphenyl)methyl]amino)hexanoic acid;
- (2S)-2-([(1S)-3-hydroxy-1-(3-methoxyphenyl)propyl]amino)-5,5-dimethylhexanoic acid;
- (2S)-2-([(1R)-3-hydroxy-1-phenylpropyl]amino)-5,5-dimethylhexanoic acid;
- 20 (2S)-5,5-dimethyl-2-([(3-(1H-1,2,4-triazol-1-yl)phenyl)methyl]amino)hexanoic acid;

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, optical isomer, N-oxide, and/or prodrug thereof.

13. A pharmaceutical composition comprising a compound according to any preceding claim and a pharmaceutically acceptable carrier, excipient, and/or diluent.

14. The compound according to any one of claims 1 to 12, or the
5 pharmaceutical composition of claim 13, for use in therapy.

15. The compound according to any one of claims 1 to 12, or the
pharmaceutical composition of claim 13, for use in the treatment or prevention of
a neurodegenerative disorder, a psychiatric disorder, an inflammatory disorder, a
cancer, pain, diabetes mellitus, diabetic retinopathy, glaucoma, uveitis,
10 cardiovascular diseases, kidney disease, psoriasis, hereditary eye conditions,
hearing loss or diseases characterized by misfolded tau;

wherein the neurodegenerative disorder is preferably selected from motor
neuron diseases, Frontotemporal Lobar Degeneration (FTLD), frontotemporal
dementia, Alzheimer's disease, Parkinson's disease, Huntington's disease, prion
15 diseases such as Creutzfeldt-Jakob disease (CJD), acute brain injury, spinal cord
injury and stroke, preferably wherein the motor neuron disease is selected from
amyotrophic lateral sclerosis (ALS), Primary Lateral Sclerosis, and Progressive
Muscular Atrophy;

wherein the neurodegenerative disorder is preferably a
20 neurodegenerative disorder characterised by misfolded TAR DNA-binding protein
43, such as amyotrophic lateral sclerosis, Alzheimer's disease, Frontotemporal
Lobar Degeneration, or frontotemporal dementia;

wherein the psychiatric disorder is preferably selected from bipolar
disorder, major depression, post-traumatic stress disorder, and anxiety disorders;

25 wherein the inflammatory disorder is preferably selected from
inflammatory diseases and neuroinflammation;

wherein the cancer is preferably selected from breast cancer, lung cancer, ovarian cancer, prostate cancer, thyroid cancer, pancreatic cancer, glioblastoma and colorectal cancer;

5 wherein the cardiovascular disease is preferably selected from atherosclerosis, cardiomyopathy, heart attack, arrhythmias, heart failure, and ischemic heart disease; and

wherein the hearing loss is preferably selected from noise-induced hearing loss, ototoxicity induced hearing loss, age-induced hearing loss, idiopathic hearing loss, tinnitus and sudden hearing loss.